The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 1 JUNE, 1941 NUMBER 6

ESTROGEN AND PROGESTIN METABOLISM IN PREGNANCY

I. SPONTANEOUS AND INDUCED LABOR[1]

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THE PHYSIOLOGICAL FACTORS concerned in the spontaneous onset of labor have been the subject of many investigations. Snyder, reviewing the literature in 1938 (1), concluded that the termination of pregnancy was subject to a timing mechanism similar to that which characterizes the length of the ovarian cycle and primarily under hormonal control. The present study was conducted in order to determine whether or not any changes in estrogen and progestin metabolism which might be of etiological significance preceded and accompanied labor and delivery. It was important, in this connection, to follow any such changes in induced as well as spontaneous delivery. The findings on urine from a woman who had false labor contractions over an 8-day period also yielded considerable pertinent information.

The steady increase in the amounts of estrogen which may be recovered from blood and urine as pregnancy advances is well known. Pregnandiol, an excretion product of progestin, has also been found in increasing amounts with advancing gestation (2). A drop in total urinary estrogens after the 38th week of pregnancy in women was first demonstrated by Marrian and coworkers in 1935 (3, 4) and has been confirmed by other investigators and ourselves (5–8). Our own studies of individual cases have indicated that labor is preceded by a period of progestin as well as estrogen withdrawal (6, 7). In individual cases, Hain (8) has found that the curves for pregnandiol excretion run parallel to those for total estrogen, the peak of excretion of both, at some time during the last 2 weeks of gestation, being followed by decreasing excretion until labor. Wide variations in the levels of excretion of both estrogens and pregnandiol, when different normal individuals at the same period of gestation are compared, have been noted by ourselves and others. It is probably for this reason that a decreasing output of pregnandiol before the onset of contractions is not apparent in the composite curve of Venning (2) on 8 cases. The only reported work on hormone excretion during labor is that of Dingemanse, Laqueur and Mühlback (9). Although their data lacks true quantitative significance, all results being expressed in I.U. per liter of urine and no allowance being made for the concentration of specimens, they indicate that estrogen excretion may decrease during labor.

In order to investigate further the drop in total urinary estrogens and pregnandiol which precedes the onset of spontaneous labor in women and to detect any changes during labor, we have separately measured urinary estradiol, estrone and estriol[2] as well as pregnandiol and have also utilized a procedure which

Received for publication March 12, 1941.
[1] The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee for Research in Problems of Sex of the National Research Council.

[2] In this and the following papers, for the sake of brevity, the "weak" phenolic non-ketonic fraction is referred to as estradiol, the "weak" phenolic ketonic fraction as estrone, and the "strong" phenolic fraction as estriol. The separation is not strictly quantitative (12) and unknown urinary estrogens may contribute to the potency of the various fractions. In late pregnancy urine, however, it is safe to interpret data on the assumption that most of the potency of each fraction is accountable to the specified estrogen.

TABLE 1. EFFECT OF MECHANICALLY INDUCED LABOR ON ESTROGEN METABOLISM
Mrs. A. C., aged 27, para I, last catamenia Feb. 7, 1940, due Nov. 14, 1940.
Labor artificially induced by rupture of membranes Nov. 14, 1940.

Date	Period of urine collection	Clinical notes	Urine analysis					
			Pregnandiol	Estriol	Estradiol		Estrone	T_{zn}/T_0
			mg./24 hr.	*mg./24 hr.*	*mg./24 hr.*	*% of* T_0	*mg./24°*	
11/12–13/40	24 hours 7:30 P.M.–P.M.	Normal	97.0	13.5	0.335	18.1	1.65	2.7
11/13–14/40	12 hours 8:30 P.M.–A.M.	Normal	95.7	14.0	0.345	17.3	2.55	2.5
11/14/40	8:30 A.M.	Rupture of membranes						
11/14/40 (1)	2 hours 8:30–10:30 A.M.	In labor		9.0	0.085	8.0	0.85	1.4
11/14/40 (2)	3 hours 10:30–1:30 P.M.	In labor		3.2	0.135	30.0	0	4.9
		Delivery at 1:30 P.M.						

appears to provide a gauge of estrogen destruction in the body. By this means we have acquired information pointing to marked changes in estrogen and progestin metabolism before and during labor. The indicated changes in metabolism give insight into the physiological significance of the decreased hormone excretion that is not revealed by less detailed studies.

EXPERIMENTAL

The data herein are derived from the study of 22 normally pregnant women during the last 10 weeks before the spontaneous onset of labor. Estradiol, estrone and estriol have been measured in 66 specimens from 15 individuals, sodium pregnandiol glucuronidate in 63 specimens from 14 cases, and estrogen breakdown products (as indicated by T_{zn}:T_0 ratios (10)) in 49 specimens from 8 patients. The composite curve of the results for each urinary constituent is represented in the charts by a heavy black line. Individual curves on 4 of the women, one of whom experienced false labor contractions, are also given. With 3 of these, complete analyses were performed on repeated specimens during labor, in order to detect any changes which might take place between the onset and the end of the second stage. In addition, one patient was followed before and after induction of labor by artificial rupture of the membranes, the results being separately given in table 1.

METHODS

In any quantitative urinalyses the collection of accurately timed specimens is, of course, of primary importance. This can be accomplished only under the most carefully supervised conditions, and even then it is our experience, particularly in hospitalized patients, that gross errors in collection frequently occur. The women who volunteered for this study were instructed and trained in the accurate collection of 24-hour samples of urine. All samples were kept cold during the period of collection and extracted on the day that collections were completed. No preservative was used. The collection of specimens over accurately timed short periods during labor was personally supervised by one of us. With 2 patients followed during labor, inlying catheters were utilized. Creatinine determinations were performed upon all specimens. Since the daily creatinine output for any individual is relatively constant,[3] any gross error in collection may by this means be readily detected. We have found such a check on the timing of collections indispensable when hospitalized patients are being followed.

Conjugated pregnandiol was gravimetrically measured according to the method of Venning (11). Estradiol, estrone and estriol were separated and extracted by the method previously described (12). Zinc hydrogenation was performed by adding 0.4 gm. of zinc and 1.5 cc. of concentrated HCl to 10 cc. of urine, boiling under a reflux condenser for 3 hours and diluting with water to 200 cc. in a volumetric flask. Due to the high estrogen content of urine of pregnancy, especially after hydrogenation, no extraction was performed and the diluted material could be assayed directly. The total estrogenic potency (in rat units) after zinc hydrogenation (T_{zn}) divided by the sum of the estrogenic potencies (in rat units) of the estradiol plus estrone plus estriol fractions (T_0) is designated as the

[3] In 10 patients trained in the accurate collection of 24-hour samples of urine and from whom repeated specimens during 4 to 6 months of pregnancy have been received, the individual averages for 24-hour output of creatinine varied from 0.96 to 1.50 gm. In no individual was the maximum deviation from her own average value greater than 25%. In the 4 cases followed during labor, however, including the patient in whom labor was induced, there was a 40 to 50% drop in the rate of creatinine excretion between the onset of contractions and delivery. The results on creatinine excretion of pregnant and non-pregnant women which have accumulated in this laboratory over the past 10 years are being separately published.

$T_{zn}:T_0$ ratio. Inasmuch as the increased potency of urine of women after hydrogenation appears to be largely accountable to the conversion of non-estrogenic materials into estrogens (10), and since the indications are that these non-estrogenic materials may be estrogen breakdown products, the $T_{zn}:T_0$ ratio is considered a relative gauge of the amount of estrogen destruction in the body.[4] The findings in this and in other of our investigations (10) are in keeping with this interpretation.

The estrogens were assayed upon mature, spayed, female rats, following a standardized modification of the Allen-Doisy procedure that is being separately published. By our technic of assay, there are 20,000 ± 5000 R.U. per mg. of estradiol, 2000 ± 500 R.U. per mg. of estrone and 2000 ± 500 R.U. per mg. of estriol. All results, including those on the 2- to 10-hour specimens during labor, are expressed in mg. per 24-hour volume of urine in order to make the values throughout these studies comparable.

RESULTS

Pregnandiol. Figure 1. The composite curve of urinary pregnandiol rises to the 38th week and drops off during the last 2 weeks before labor. The individual curves demonstrate that the peak may come anywhere between 24 and 8 days before contractions start and that the drop prior to the onset of labor may, in some individuals, be less marked than would appear from the composite curve. The 3 women followed during the first and second stages of labor showed a progressive decrease in urinary pregnandiol, the most striking drop coming during the second stage.

One individual, *D.Y.*, had false labor between the 22nd and 14th days before true labor began. After 2 days of mild contractions, urinary pregnandiol was unmistakably diminished. This observation, together with the progressive decrease during true labor, shows that, although true labor follows a drop in pregnandiol excretion, uterine contractions themselves are accompanied by a further and more rapid decrease in the output of this product of progestin metabolism.

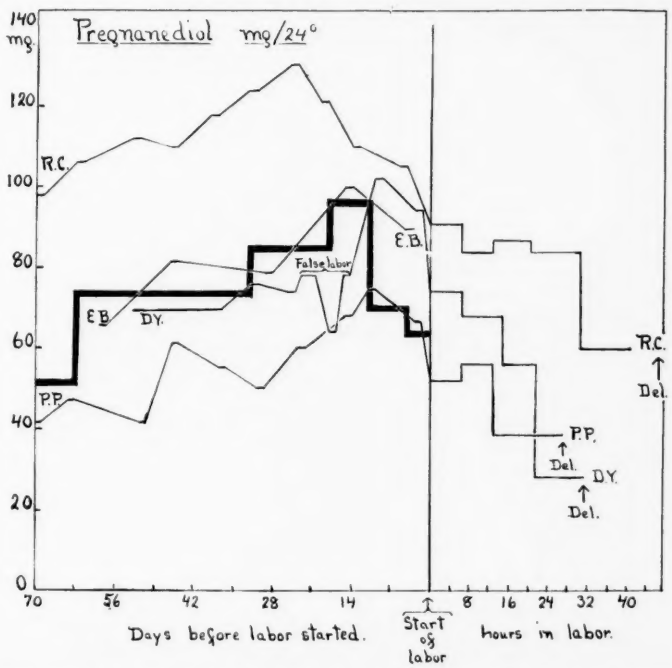

Fig. 1. URINARY PREGNANDIOL DURING THE LAST 10 WEEKS OF NORMAL PREGNANCY AND DURING LABOR. Heavy black line =composite curve based on 63 specimens from 14 individuals followed to term.

Estriol. Figure 2. Evidence is accumulating that in women as in rabbits (22) estriol is the end product of the conversion of estradiol to estrone to estriol and that the irreversible estrone to estriol conversion is facilitated by the presence of adequate progestin (6, 7, 13). The level of urinary estriol, therefore, when considered in the light of the other urinary estrogens, provides an index of progestin secretion and utilization. Figures 1 and 2 demonstrate that estriol and pregnandiol excretion run parallel during the last 10

[4] Although, theoretically, the titer of unextracted aqueous solutions, as performed upon zinc hydrolyzed late pregnancy urines, should not be compared with the titer of olive oil extracts of the separated fractions after acid hydrolysis, actually this procedure has been found to give $T_{zn}:T_0$ ratios which do not differ significantly from those acquired if the zinc hydrolyzed urine is assayed in olive oil.

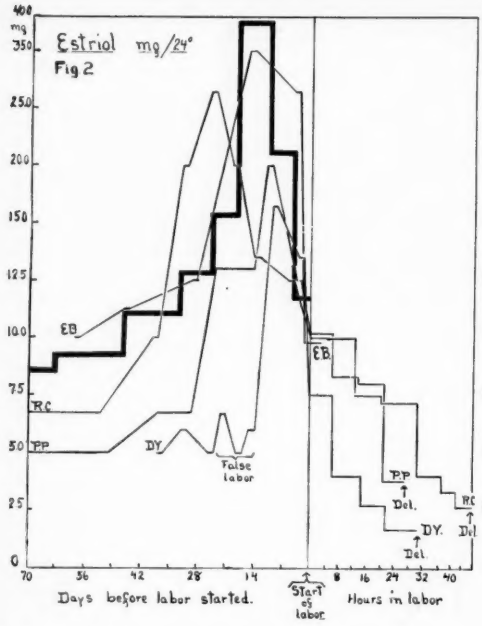

Fig. 2. URINARY ESTRIOL DURING THE LAST 10 WEEKS OF NORMAL PREGNANCY AND DURING LABOR. Heavy black line = composite curve based on 66 specimens from 15 individuals followed to term.

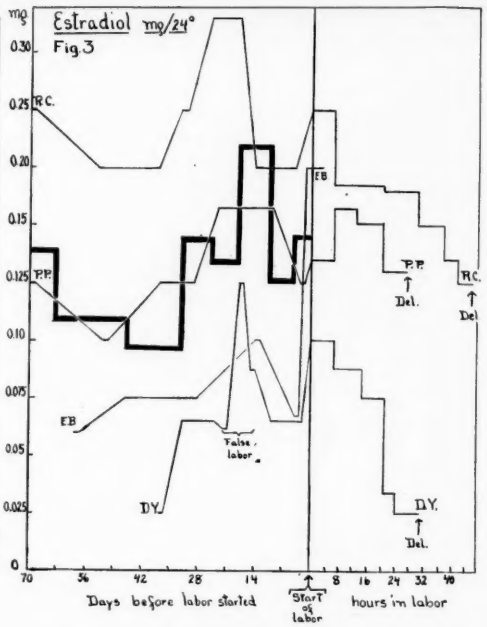

Fig. 3. URINARY ESTRADIOL DURING THE LAST 10 WEEKS OF NORMAL PREGNANCY AND DURING LABOR. Heavy black line = composite curve based on 66 specimens from 15 individuals followed to term.

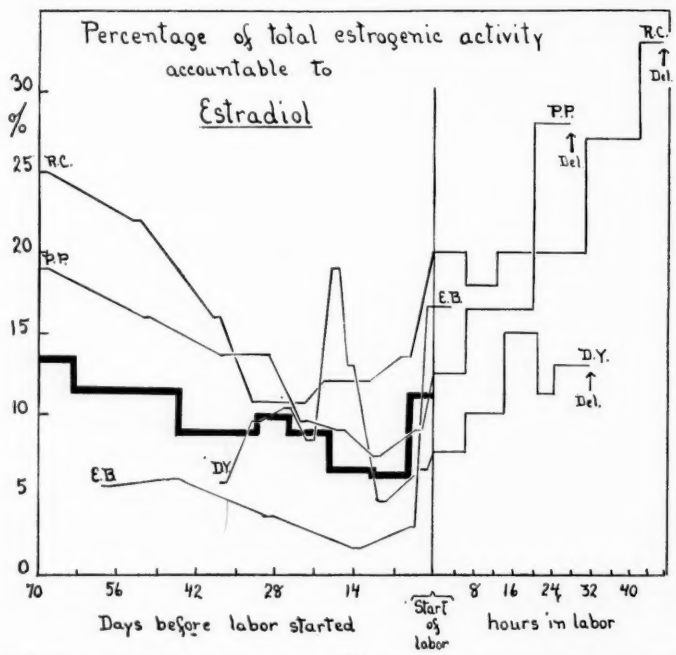

Fig. 4. PERCENTAGE OF TOTAL ESTROGENIC POTENCY OF URINE (T_0) ACCOUNTABLE TO ESTRADIOL DURING THE LAST 10 WEEKS OF NORMAL PREGNANCY AND DURING LABOR. Heavy black line = composite curve based on 66 specimens from 15 individuals followed to term.

weeks of normal pregnancy. In both the composite and individual curves, the time of the peak in estriol excretion coincides with that in urinary pregnandiol and is followed by the same interval of decreasing excretion prior to labor. After the onset of contractions, there is an immediate and rapid decrease in the rate of estriol excretion. Furthermore, false labor in *D.Y.* was accompanied by a transitory drop in the excretion of estriol. It would appear, therefore, that the spontaneous onset of true labor is preceded by diminished production of progestin with a consequent and concomitant decrease in the rate of estrone to estriol conversion, and that uterine contractions in themselves are associated with a further and even more pronounced effect of a similar nature upon estrogen and progestin metabolism.

Estradiol. Figures 3 and 4. Estradiol is probably the primary estrogen secreted both in the pregnant and non-pregnant woman (7, 13–16). The indications are that the rate of conversion into estrone depends upon the rate of the irreversible estrone to estriol reaction (7, 13). A rise in the level of urinary estradiol, therefore, might reflect either accelerated production or a reduced rate of estradiol to estrone to estriol conversion due to progestin deficiency. Interpretation of results on urinary estradiol, therefore, must depend upon the levels of the other estrogens. This is best demonstrated by expressing estradiol in terms of percentage of total estrogenic activity accountable to this estrogen (fig. 4). During the period when urinary pregnandiol and estriol are rising to peak levels, there is also great augmentation of estradiol excretion. Figure 4 demonstrates, however, that the percentage of total estrogenic activity accountable to estradiol is steadily decreasing over this interval. The interpretation would be, therefore, that the rise in estradiol is due to increasing production and that this process is being accompanied by an accelerated rate of estradiol to estrone to estriol conversion due to increasing progestin secretion. Following the peak period, the drop in urinary estriol and pregnandiol is accompanied by a falling off of estradiol excretion. In all of the individual curves of figure 4 it may be noted that a slight rise in the percentage of activity accountable to estradiol occurs during this same interval, from which we would infer that decreasing production is being accompanied at this time, days 13 to 3 before labor, by some decrease in the rate of conversion. A sudden marked rise in urinary estradiol was found to accompany the onset of spontaneous true labor. Inasmuch as this applies to the percentage figures also, we conclude that it reflects a sudden decrease in the rate of conversion, and possibly an increased production as well.

The progress of true labor was consistently accompanied by a decreasing rate of excretion of estradiol together with increasing percentages of total activity accountable to this estrogen. As true labor progressed to delivery, therefore, there is evidence for a further decrease in the supply of estrogen and progestin and an even more rapid drop in the rate of estradiol to estrone to estriol conversion. The specimen from *D.Y.* collected after 2 days of false labor contractions, also reflected a decreased rate of conversion, apparently the result of a drop in progestin, but the rise in actual amount of estradiol excreted, in contrast to the drop during true labor, would indicate that the comparatively mild contractions had been followed by no depression of the supply of estrogen. This finding may be of considerable significance in connection with the fact that the transient progestin deficiency in this patient (seemingly a result of uterine contractions) appeared to be self-corrected and the pregnancy progressed normally from the 38th week to term.

Estrone and $T_{zn}:T_0$ ratio. Figures 5 and 6. Estrone is the most readily oxidized of the naturally occurring estrogens in women (10 and unpublished observations). There is reason to suppose that estrogen destruction in the body is an oxidative process (Marrian, G. F., Harvey Lectures, 1939). Since adequate progestin prevents estrogen destruction, one would expect a progestin deficiency to be accompanied by low values for urinary estrone. Progestin, on the other hand, facilitates estrone to estriol conversion, so that low values for urinary estrone might reflect a high level of progestin activity with a consequent removal of estrone from the circulation by its conversion into estriol. Figure 5, therefore, can be interpreted only in the light of the other urinary findings. $T_{zn}:T_0$ ratios, figure 6, appear to provide a gauge of estrogen destruction in the body (10). In discussing the observed changes in estrone excretion, we must refer to this as well as the other 4 charts, and must also consider our uncharted data on the percentage of total estrogenic activity accountable to estrone.[5]

With each of the individuals in whom repeated analyses for the separated estrogens were performed, the specimen which contained the most estriol also gave the highest value (in mg.) for estradiol and estrone (the only exception being *D.Y.*, in whom the findings were complicated by false labor). In the composite curves also the peak values for all 3 estrogens coincided during the 38th week. During this same period, both in the composite and individual curves, the highest levels of pregnandiol excretion, the lowest figures for percentage of activity accountable to estra-

[5] The percentage figures for estriol need not be considered, since most of the estrogenic activity of pregnancy urines is accountable to this estrogen, and therefore the values for percentage activity vary over rather narrow limits and reveal nothing not demonstrated by those for mg. in 24 hours. The composite curve for the percentage of total activity accountable to estriol, even including the values during labor, lies between 80 and 90%.

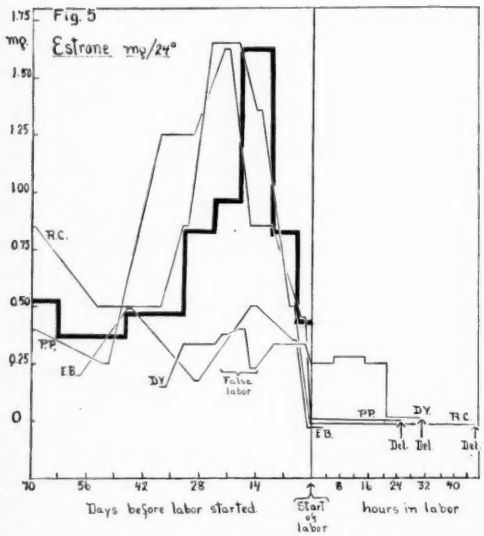

Fig. 5. URINARY ESTRONE DURING THE LAST 10 WEEKS OF NORMAL PREGNANCY AND DURING LABOR. Heavy black line = composite curve based on 66 specimens from 15 individuals followed to term.

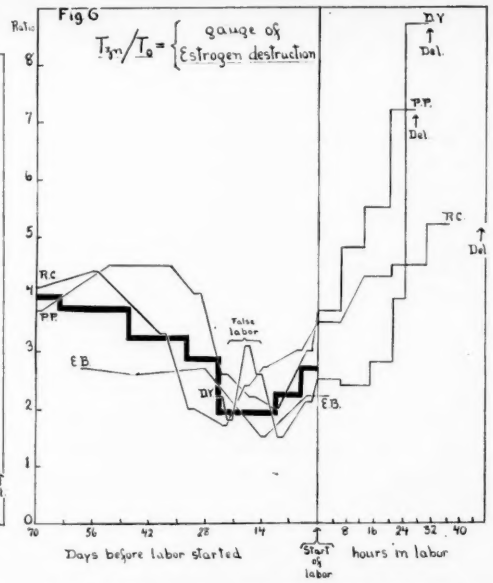

Fig. 6. RATIO OF TOTAL ESTROGENIC POTENCY OF URINE AFTER ZINC HYDROGENATION (T_{zn}) TO TOTAL ESTROGENIC POTENCY AFTER ACID HYDROLYSIS (T_0) DURING THE LAST 10 WEEKS OF NORMAL PREGNANCY AND DURING LABOR. Heavy black line = composite curve based on 49 specimens from 8 individuals followed to term.

diol and the lowest $T_{zn}:T_0$ ratios occurred. Furthermore, the urines collected at this time showed a drop in the percentage activity accountable to estrone. Considered in relation to the other findings, this last observation must reflect an increased rate of estrone to estriol conversion with a consequent decrease in the rate of destruction. At around the 38th week of normal pregnancy, therefore, we have evidence for a maximum production of estradiol, a maximum rate of estradiol to estrone to estriol conversion, and a minimum rate of destruction of the estrogens, which, together with the high pregnandiol excretion, must reflect a maximum production of progestin also.

During the interval between the time of this peak in the efficiency of estrogen and progestin metabolism and the onset of labor, there is a precipitous drop in estrone excretion. This is accompanied by a gradual falling off of the percentage activity accountable to estrone and a slight rise in the $T_{zn}:T_0$ ratios. From the data in figures 1 through 4 we have concluded that this period is one of decreasing production of both estrogen and progestin and a gradual decrease in the rate of conversion. From figures 5 and 6, considered in the light of the other findings, we infer that the drop in estrone reflects some increase in the rate of estrogen destruction over this interval before labor starts, as well as decreasing estrogen production.

The onset of true labor is accompanied by a sudden marked drop in estrone excretion and rise in $T_{zn}:T_0$ ratios. In 3 of the 4 cases studied at this time, estrone disappeared completely. From these observations, in conjunction with the findings discussed above, we would conclude that the onset of true labor is associated with a rapid decrease in the rate of conversion together with a rapid increase in the rate of destruction of the estrogens. It seems possible that this striking change in estrogen metabolism, an exact parallel of the situation at the start of normal menstruation (13), may be of etiological significance in the onset of contractions.

Estrone was not demonstrable in any of the labor specimens except those collected during the first stages from *D.Y.*, and disappeared from the urines of this patient during the last 10 hours before delivery. Absence of any demonstrable estrone has invariably been associated with other findings indicating rapid destruction of the estrogens. The tremendous rises in $T_{zn}:T_0$ ratios during labor must be accountable to the presence of estrogen breakdown products. During false labor, also, there was evidence for an increased rate of estrogen destruction, though not as marked as was apparent prior to delivery. Taken as a whole, the data suggest that uterine contractions in themselves may amplify a change in estrogen and progestin metabolism which has been steadily progressing for about 2 weeks before their inception, namely, a decreasing supply of estrogen and progestin with the consequent failure in conversion and rapid destruction of the estrogens. Considering the previously published indications (7) that estrogen facilitates the me-

tabolism and prevents the destruction of progestin, the drop in urinary pregnandiol before and during labor probably reflects progestin destruction as well as decreased production.

The onset of false labor. The results on the urine specimen collected from *D.Y.* at the onset of false labor reflect a qualitatively normal situation for the period of pregnancy at which it occurred, that is, evidence for an increase in estrogen and progestin production with the accompanying increase in rate of conversion and decrease in rate of destruction of the estrogens. There is some indication, however, that the hormonal situation in this patient during the interval followed prior to the start of false labor was not entirely normal. Total estrogen in this individual, up to the 8th day before true labor, was lower than in any other normal pregnancy followed at this period of gestation. This in itself is less significant than the fact that up to the 14th day prior to true labor there was no evidence for the steady and rapid rise in estriol and pregnandiol excretion seen in the other normal pregnancies at some time prior to 14 days before term. Furthermore, this is the only case in whom a rise in the percentage activity accountable to estradiol occurred at this stage of gestation. These findings indicate that the rate of increase in estrogen and progestin production and conversion in *D.Y.* was not as great during the period which normally precedes peak values as was found in the other cases. It was at this period that false labor occurred. Although the results at the start of this episode lead us to conclude that uterine contractions may be initiated without the striking change in estrogen and progestin metabolism which characterizes the onset of true labor, it is possible that increased sensitivity of the uterine musculature at the time of rapid growth of the products of conception was, in this individual, a result of a comparative hormonal deficiency. The fact that contractions stopped when the urinary findings reflected a marked increment in estrogen and progestin production and conversion again shows a close relationship between steroid metabolism and the sensitivity of the uterine musculature.

Artificially induced labor. Table 1. The fact that labor may be mechanically induced is fairly good evidence that uterine contractions may be initiated by factors other than hormonal. Only by studying induced labor could we determine whether or not uterine contractions in themselves would produce the rapid change in estrogen and progestin metabolism which accompanies spontaneous labor. The results of such a study (table 1) answered this question in the affirmative and were of considerable importance in broadening our conception of the train of events in this changed metabolism of the steroids as well as possible causes for its inception.

The 2 control specimens, covering the 37 hours before artificial rupture of the membranes, gave check values (within the range of experimental error) for all of the constituents measured except estrone. Considering the fact that there was no other evidence for changing metabolism over this short period we would hesitate to attach any significance to the rise in estrone. The high values for estrone in both of the control specimens suggest that the changes which characteristically precede spontaneous contractions were not in progress, among them being a drop in estrone due to an increasing rate of estrogen destruction. All of the other findings, however, were within the range of values found in the urines of normal women at or near term, and the estrone figures may well have been lower at this time than at an earlier date. Only by repeated analyses over a longer interval could we have determined whether or not spontaneous labor was imminent.

The membranes were ruptured at 8:30 A.M. and uterine contractions started immediately. The specimen which covered the first 2 hours of labor showed a truly amazing drop in the level of all 3 estrogens, particularly estradiol. (There was not enough urine during this short labor for pregnandiol determinations.) The data on this first labor urine give striking evidence for an immediate depression of estrogen production after the onset of mechanically induced contractions. This rapid drop in the supply of estrogen must have been the direct result of uterine contractions, probably through embarrassment of placental circulation.[6] During this 2-hour interval, however, there was no evidence for progestin deficiency; in fact the drop in percentage activity accountable to estradiol would indicate an increased rate of conversion, and the lowered $T_{zn}:T_0$ ratio a decreased rate of destruction. The specimen collected over the following 3 hours, which included the catheter specimen at delivery, gave evidence of progestin as well as estrogen deficiency, namely, a further drop in estriol associated with a rise in the percentage activity accountable to estradiol, a disappearance of estrone and a rise in the $T_{zn}:T_0$ ratio.

In all of our studies we have had evidence that estrogen and progestin are mutually interdependent for their conversion and protection against destruction (7). A deficiency of either has been invariably accompanied by evidence for a deficiency of the other and it has been impossible to determine which came first. The findings over this short period of labor indicate that in this case estrogen withdrawal preceded progestin deficiency. They demonstrate that uterine contractions themselves, presumably through embarrassing the placental circulation, had an immediate de-

[6] Reynolds and Foster (17) have shown that the efficiency of the flow of maternal blood through the placenta is dependent upon intrauterine pressure. Uterine contractions must, of course, produce a sudden marked increase in intrauterine pressure and a consequent embarrassment of placental circulation.

pressant effect upon the supply of estrogens and that this estrogen withdrawal was followed by the typical progestin deficient metabolism of the estrogens. The results on this case are of particular significance in relation to possible primary causes for the progestin deficient metabolism of the estrogens in late pregnancy toxemias, and will be referred to in the following paper of this series.

DISCUSSION

The theoretical implications of the findings presented defy adequate discussion. Their relation to acetylcholine, cholinesterase and hypophyseal physiology must be intimate. The principal items to be considered, however, are (*a*) possible causes for the prepartum drop in estrogen and progestin and (*b*) the question of whether or not the marked changes in steroid metabolism which precede and accompany labor may be responsible for parturition. The results of this study are also extremely pertinent in relation to the preeclamptic and eclamptic syndrome, but this phase of the discussion will be left for the following paper of this series.

(*a*) We have seen that the drop in estrogen and progestin which progresses for some 2 weeks prior to the onset of spontaneous labor is preceded by a period around the 38th week, of maximum production, maximum rate of conversion and minimum destruction of the estrogens, which, together with the high pregnandiol excretion, indicate a maximum production of progestin also. Is this peak in the production of these two steroids and the consequent peak in the efficiency of their metabolic conversion rather than degradation in any way responsible for the following period of decreasing production which precedes normal labor?

The findings during these two periods of late pregnancy are entirely analogous to those during the luteal and premenstrual phases of the normal ovarian cycle of non-pregnant women (10, 13). From the blood, urine, endometria and menstrual discharge of non-pregnant women, we have recovered a factor which stimulates preformed corpora lutea to increased and prolonged activity (18). (The recovery of a similar substance from rat placentas has been reported (19).) Our corpus luteum stimulating extracts have been found to contain no known gonadotropic hormone and no demonstrable estrogen. Zinc hydrogenation of these extracts, however, has resulted in the formation of considerable amounts of estrogenic material. The administration of estrogen to rodents characteristically stimulates preformed corpora lutea to increased functional activity. That this corpus luteum stimulating factor may be a conjugated estrogen breakdown product is suggested, first, because it appears in the highest concentrations in the blood and urine of women at the time when estrogen destruction is at its maximum, i.e., during menstruation (10, 13), secondly, because it duplicates an effect which is characteristic of estrogen itself, i.e., corpus luteum stimulation, and, thirdly, because zinc hydrogenation of this non-estrogenic material produces estrogenic activity. It has naturally occurred to us that the corpus luteum stimulating effect ascribed to the estrogens may actually be accountable to a conjugated estrogen breakdown product. On this basis, the high rate of progesterone secretion during the luteal phase of the normal cycle and around the 38th week of normal pregnancy could be considered as being actually responsible, because of the resultant more complete conversion of estrogens and lowered concentration of estrogen breakdown products, for the regression of the corpus luteum which precedes menstruation and the decreasing progesterone and estrogen secretion during the period prior to spontaneous labor. Heckel and Allen (20) have concluded that parturition in the rabbit is preceded by decline of the corpus luteum and that this decline may be due to a failing supply of estrogen. The above considerations would take us one step farther in suggesting that the failing supply is not in estrogens themselves but in estrogen breakdown products. In other words, the peak of progesterone secretion may be considered as bringing about its own reduction. If this hypothesis is correct, one must assume that the concentration of breakdown products during the period of estrogen and progestin withdrawal, although increasing slightly, is never great enough to prevent continued reduction. The findings presented above are in keeping with this assumption.

(*b*) The changes in steroid metabolism which precede spontaneous labor reflect a progressive progestin deficiency. Heckel and Allen (20) have presented a sound basis for their contention that parturition in the rabbit is precipitated by a decline of progestin secretion. Reynolds and Foster (17, 21), working also with rabbits, have demonstrated that, in the last stages of pregnancy, uterine distention does not keep pace with the growth increments of the fetus, the result being a final rapid increase of pressure on the placental vascular bed with a consequent decrease in the flow of maternal blood through the placenta. These two theories of parturition, the one hormonal and the other mechanical, are not incompatible. Reynolds has found that "when estrin is the predominant hormone the capacity of the distended uterus to grow is appreciably reduced" (21). Our findings show that "when estrin is the predominant hormone," ie., produced in the absence of adequate progestin, it undergoes degradation rather than metabolic conversion. The fact that uterine growth during the last stages of pregnancy does not keep pace with fetal growth may well be related to this changing metabolism of estrogens due to a progressive progestin deficiency. On this ba-

sis, the increased intrauterine pressure at term would be primarily due to progestin withdrawal. We have seen, however, that increased intrauterine pressure in itself is capable of producing a progestin deficient metabolism of the estrogens with failure in conversion and rapid destruction. In artificially induced labor, the primary stimulus for contractions must be mechanical. It seems probable that under normal conditions the hormonal changes come first, but, in any event, the final result must be the establishment of a vicious circle, which would inevitably lead to a progressive failure in blood supply to the placenta and increase in the rate of destruction of placental steroids. (In the case of false labor (*D.Y.*), there was evidence that the comparatively mild contractions did not depress estrogen production and that, perhaps for this reason, sufficient progestin secretion was developed to cut in upon the vicious circle by facilitating estrogen utilization for uterine growth and distention, thereby re-establishing the placental blood supply.)

Since the changes in steroid metabolism before and at the time of menstruation are similar to those before and at the onset of labor and since vasoconstriction in the endometrium is the most striking premenstrual phenomenon, one might think of vascular spasm as an incitant to labor contractions.

We have seen that the uterine contractions of true labor, whether spontaneous or induced, result both in a rapidly diminished supply and a rapid destruction of estrogen and progestin. Could the sudden withdrawal of the placental steroids be responsible for the final act of delivery? We know that estrogen and progestin withdrawal releases anterior pituitary hormones, for example, the lactogenic hormone after delivery in all species and gonadotropic substance in many, as demonstrated by their postpartum ovulation. One might suggest that the slow withdrawal of estrogen and progestin before labor and their rapid withdrawal during labor also release progressively greater amounts of pituitrin, and that this factor provides the final contractile stimulus by its direct effect both on arterioles and uterine muscle.

SUMMARY

Analyses of urine specimens from 22 normally pregnant women during the last 10 weeks of pregnancy have revealed that at some time between 8 and 24 days prior to labor a maximum efficiency in the production and conversion of estrogen and progestin is reached.

Between this peak period and the onset of labor a progessive change in steroid metabolism takes place, characterized by progestin and estrogen withdrawal and accountable to a gradually decreasing rate of production and conversion and some increase in the rate of destruction of these placental steroids.

The onset of true labor, in the 4 cases followed at this time, coincides with evidence for a sudden decrease in conversion and increase in destruction of estrogens.

Findings on one patient who experienced false labor reveal that, although uterine contractions may be initiated without any evidence for a sudden increase in estrogen destruction, a relative hormonal deficiency at the period which is normally one of maximum production and conversion may increase the sensitivity of the uterine musculature.

Uterine contractions themselves result in a rapid reduction in the rate of estrogen and progestin production and conversion and a striking increase in their rate of destruction. This same change in steroid metabolism was apparent during a 5-hour period of labor artificially induced by rupture of the membranes.

Possible causes for the prepartum withdrawal of estrogen and progestin and the physiological significance of the changes in steroid metabolism which precede and accompany labor are discussed.

We are indebted to the women who volunteered for this study, to their obstetricians, Drs. Christopher J. Duncan, Spencer C. Flo, Samuel B. Kirkwood, John Rock, Judson A. Smith and Raymond S. Titus, and to the nursing staffs of the Boston City Hospital, the Boston Lying-in Hospital, the Baker Memorial Hospital and the Florence Crittenton Home.

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II. THE ENDOCRINE IMBALANCE OF PREECLAMPSIA AND ECLAMPSIA. SUMMARY OF FINDINGS TO FEBRUARY, 1941[1]

ESTROGEN AND PROGESTIN METABOLISM IN PREGNANCY

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SINCE the last publications from this laboratory (1,2) on hormonal investigations in human pregnancy, 18 additional cases have been studied. Three of these were normal late pregnancies;[2] 13 had preeclampsia and 2 eclampsia. The object of the present communication is to report the data from these recent cases in combination with our earlier data, to bring our results from the quantification of serum chorionic gonadotropin (CG) up to date and to summarize our evidence that a progestin deficient metabolism of the estrogens is a characteristic feature of the preeclamptic syndrome.

The methods used for following estrogen and progestin metabolism are discussed in the preceding paper. The technic for approximately gauging the level of serum CG has been described (1). As was emphasized, the assay is not truly quantitative and a given patient should be considered as having high or low values only when check results are obtained on at least 2 specimens of serum.

Serum Chorionic Gonadotropin

The values for serum CG on 173 pregnancies studied from 1932 through February, 1939, have been summarized (1). The 3 normal cases since studied (a total of 25 analyses during the last 8 to 12 weeks of pregnancy) consistently had normal CG, i.e., 100 R.U. or less per 100 cc. to within 4 weeks of term, when a rise to 200 R.U. or over is sometimes observed. Of the 15 previously unreported cases having preeclampsia or eclampsia (51 analyses) 3 with diabetes and 6 without diabetes had elevated serum CG. (In the 3 cases of this high CG group followed from earlier in pregnancy, an abnormal rise had been detected 4 to 8 weeks prior to the development of toxemia.) There was no question of the diagnosis in the remaining 6 cases with normal CG.[3] Five had severe preeclampsia and one eclampsia. None had had any toxic signs before the 21st week. Despite their normal CG values, these patients, as well as the 9 with high serum CG, gave evidence, on urinalysis, of the typical progestin deficient metabolism of the estrogens (v.i.).

The present totals for serum CG are summarized in table 1. Though not a consistent abnormality, high serum CG usually characterizes preeclampsia and eclampsia and is frequently found in patients who deliver prematurely. From our relatively small experience, 16 cases, it always characterizes late pregnancy toxemia in diabetes. In no pregnancies followed from early in gestation that were normal and remained normal, 39 including 10 diabetics, have we found elevated serum CG between the 20th and 36th week. The detection of unmistakably high values in otherwise normal patients during this period has always been followed by later trouble. Of 35 such cases, 28 developed preeclampsia and 7 delivered prematurely.

Received for publication March 12, 1941.

[1] The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee for Research in Problems of Sex of the National Research Council.

[2] These are the 3 cases in the first paper of this series, in which hormonal changes were followed through the second stage of labor.

[3] Serum CG analyses had not been performed on any of these 6 patients before the appearance of severe toxemia. One died of eclampsia a day after the only blood specimen was taken. That high CG values may have existed at an earlier date in these patients and become depressed at the time of study because of toxemia is suggested by a recent case (January, 1941). This patient, a diabetic in whom weekly serum CG analyses had been performed starting at the 32nd week of pregnancy, showed no toxic signs until the 37th week, when a little urinary albumin and an excessive gain in weight were noted. The CG during this interval (5 analyses) was clearly elevated, varying between 500 and 1000 R.U. per 100 cc. of serum. In the 38th week, severe preeclampsia supervened. During this episode the serum CG was only 100 R.U. This case is not included in the present series, since the assays of the urinary estrogens are not yet completed.

TABLE 1. SERUM CHORIONIC GONADOTROPIN ANALYSES IN LATE PREGNANCY
Summary to January, 1941. 191 Cases

Diagnosis	No. of cases	Normal CG	High CG
Normal pregnancy	67	67	0
Preeclampsia	80	13, 16.3%	67, 83.7%
Eclampsia	20	3, 15%	17, 85%
Nephritis	9	9	0
Essential hypertension	2	2	0
Premature delivery, 6–8 months	13	5, 38.5%	8, 61.5%

Estrogen and Progestin Metabolism

Comparatively low levels of 'estrin' in the blood and urine of patients with late pregnancy toxemia were first reported by us in 1933 (3). Some investigators (4, 5, 6, 6a) have confirmed this observation, whereas others (7, 8, 9) have recorded high or normal values. The same discrepancy between the results of various laboratories exists concerning pregnandiol excretion in preeclampsia and eclampsia. Our own findings (2, 10 and text below) indicate a progestin deficiency in such cases. Some (6a, 11) have reported low values for urinary pregnandiol in late pregnancy toxemia; others, however (8, 12), have found high or normal values. This failure in agreement is readily understood when certain factors are considered. In the first place, the collection of accurately timed urine specimens is of primary importance. Secondly, our own data and those of others (8, 13) demonstrate the wide range of total estrogen and pregnandiol in the urine during the last 12 weeks of normal pregnancy when one individual's values are compared with another's, and point out the necessity of repeated analyses in a given case for detecting an abnormal situation, i.e., decreasing rather than the normally increasing values for these substances as pregnancy progresses to around the 38th week. Finally, by the methods utilized in the present investigation, namely, separation of total estrogen into its components and zinc hydrolysis, a progestin deficient metabolism of the estrogens may be detected, this information being of much greater significance than either the actual levels or curves of excretion of total estrogens and pregnandiol. Although many of the specimens from the 22 cases of toxemia covered in this report contained amounts of total estrogen and pregnandiol within the range of our normal values, in only one did we fail to find definite evidence throughout the period of study for a progressive progestin and estrogen deficiency. (In this patient (v.i.), toxic signs were mild and transient and the endocrine changes indicated that the condition was self-corrected.)

Our data to date concerning 15 normal and 22 toxemic cases on whose urines during the last 13 weeks of pregnancy complete analyses have been performed, i.e., for pregnandiol, separated estrogens and T_{zn}:T_0 ratios,[4] are summarized in the accompanying charts. The analyses on 2 of the normals and 8 of those with toxemia have been partially reported in earlier papers (2, 10, 15). Of the 22 toxemic cases, 15 were diagnosed as having preeclampsia grade 2 (symptoms as well as signs), 4, preeclampsia grade 1 (signs without symptoms) and 3, eclampsia. Two of those with eclampsia died and the diagnosis was confirmed at autopsy. None of the 22 had had any clinical manifestations of toxemia prior to the 21st week of pregnancy.

The results of urinary studies on 3 cases with diabetes to whom hormones were administered prior to the development of toxic signs are omitted, although they gave evidence of the progressive changes indicating progestin deficiency and all 3 patients had toxic signs at a later period. Two were included in a previous report (2). Five of the 22 toxemic cases of this report had diabetes, namely, the 4 with preeclampsia grade 1 and 1 with preeclampsia grade 2. There is nothing in our findings on estrogen and progestin metabolism to differentiate between diabetics with preeclampsia and nondiabetics with the same syndrome. Those with diabetes have in general had less severe toxemia, but this may well be accountable to the fact that in all of them pregnancy was interrupted 3 to 4 weeks before term and 4 of them received large amounts of estrogen and progestin starting within a week of the onset of clinical manifestations. We suspect that many women, particularly diabetics, with the hormonal imbalance typical of preeclampsia, have premature delivery or intrauterine death, often with no signs that would be recognized clinically as preeclampsia, at a time when others develop toxemia (1, 2, 16). We also suspect, from earlier findings (16) and from more complete studies on a diabetic of this series with preeclampsia grade 1 (*Mrs. A. L.* in the charts), that mild toxic signs in some women may be accompanied or preceded by a progestin deficient metabolism of the estrogens which is self-corrected.

Presentation of Results (fig. 1–6)

Explanation. The shaded area on each chart covers the range of values found in the normal pregnancies. The range of normal values for weeks 27–30, that for weeks 31–33, that for weeks 34–35 and those for each succeeding week, term and labor are each based on the analyses of 5 to 9 specimens of urine, with the exception of figure 6, in which the ranges for weeks 34–35 and 38 are based on only 3 specimens apiece. The heavy line represents the average of the normal values during each period. Results on individual specimens from toxemic patients are marked by (*a*) dots, which mean that clinical manifestations were present when the specimen was collected, (*b*) circles, to indicate absence of clinical evidence for toxemia at the time of collection and (*c*) ringed dots, which mean the patient had eclampsia. Lines connect values on repeated specimens from the same individual. The heavy dotted line is a composite of (*a*) and (*c*).

Pregnandiol (fig. 1). Although the assays of some of the preeclamptic urines fall within the normal range, the evidence shows low levels of this substance to be a general characteristic of these cases. Furthermore,

[4] That is, ratio of total estrogenic activity after zinc hydrolysis to total activity after acid hydrolysis—interpreted as a gauge of estrogen destruction—see preceding paper and ref. 14.

when repeated assays were performed on urines from the same individual, decreasing rather than normally increasing amounts were found as pregnancy advanced.

The only exception was a diabetic, *A. L.*, who had slight hypertension and edema and a very slight amount of urinary albumin for about 3 weeks, all of which had practically disappeared by the 33rd week on routine care, when normally increasing pregnandiol excretion was determined. Her diabetes was severe and she was nearly blind from retinal separation. No urinalyses were performed after the 35th week. During the 37th week, mild signs of toxemia reappeared. Cesarean section was performed. The baby appeared vigorous and normal but died 3 days later, the diagnosis at autopsy being interstitial pneumonia and pulmonary edema. Other hormonal findings on this case and their possible significance will be discussed below.

Estriol (*fig. 2*). The fact that estriol and pregnandiol excretion run parallel in normal pregnancy was demonstrated in the preceding paper. In preeclampsia the same situation appears to hold as regards both individual and composite curves. Low values for urinary estriol are seen to be a general characteristic of preeclampsia and eclampsia, and repeated specimens on individuals (with the exception of *A.L.*, v.s.) reveal decreasing rather than the normally increasing levels with advancing gestation. Since the rate of conversion of estradiol to estrone to estriol appears to be dependent upon progestin, the observed parallelism in pregnandiol and estriol excretion in preeclampsia and eclampsia point to an actual and progressive progestin deficiency in this disease.

Estradiol (*fig. 3, 4*). From our previous work on estrogen metabolism in women (2, 10), we have deduced that estradiol is the primary estrogen, both in ovarian and placental physiology, and that the reversible estradiol to estrone conversion is dependent upon the rate of the irreversible estrone to estriol reaction. As was pointed out in the first paper of this series, the percentage of total estrogenic activity of urine accountable to estradiol gives more information

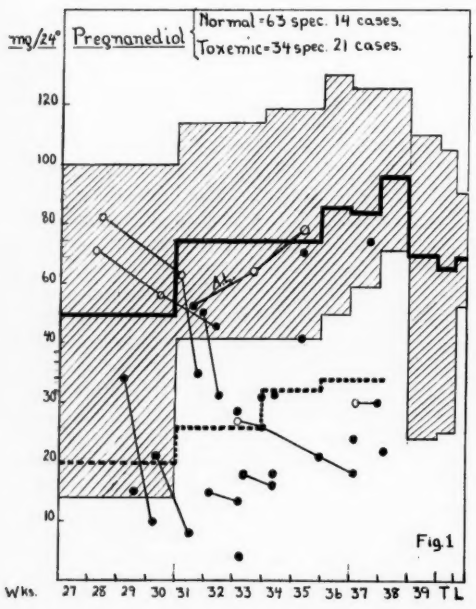

Fig. 1. Urinary pregnandiol in normal pregnancy and preeclampsia (mg. per 24° volume)

Shaded area = range of normal values; heavy line = composite curve of normal values; dots = individual specimens from preeclamptics at the time of clinical manifestations; circles = individual specimens from preeclamptics at times when toxemia was not clinically apparent; heavy dotted line = composite curve of values on patients with clinical manifestations of preeclampsia; lines connect values on repeated specimens from the same individual. T = term, i.e., within 5 days of labor; L = during labor.

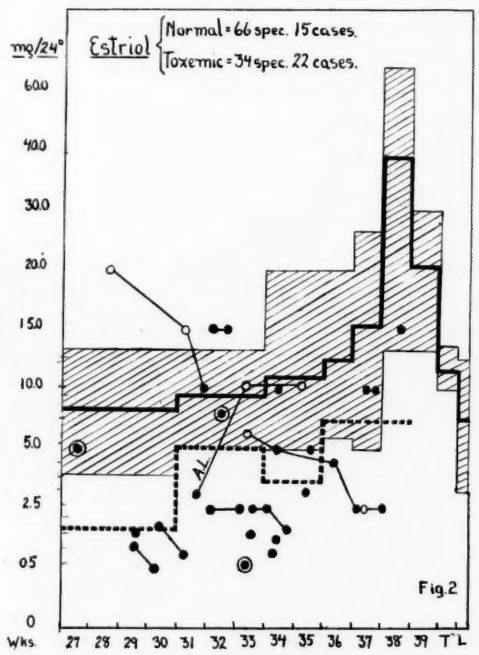

Fig. 2. Urinary estriol in normal pregnancy, preeclampsia and eclampsia (mg. per 24° volume)

Shaded area = range of normal values; heavy line = composite curve of normal values; dots = individual specimens from preeclamptics at the time of clinical manifestations; circles = individual specimens from preeclamptics at times when toxemia was not clinically apparent; ringed dots = specimens from eclamptics; heavy dotted line = composite curve of values on patients with clinical manifestations of preeclampsia or eclampsia; lines connect values on repeated specimens from the same individual. T = term, i.e., within 5 days of labor; L = during labor.

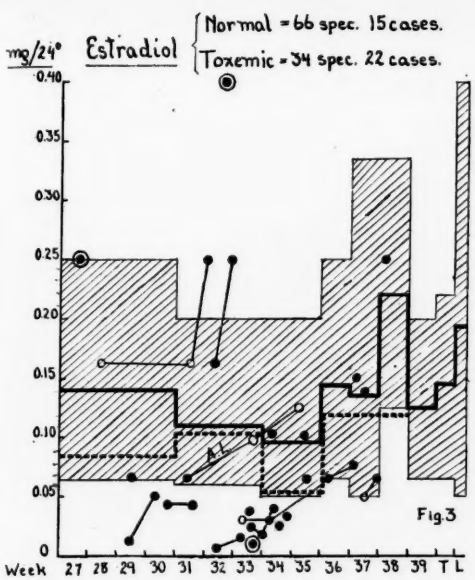

Fig. 3. Urinary estradiol in normal pregnancy, preeclampsia and eclampsia (mg. per 24° volume).
For explanation of symbols, see figure 2.

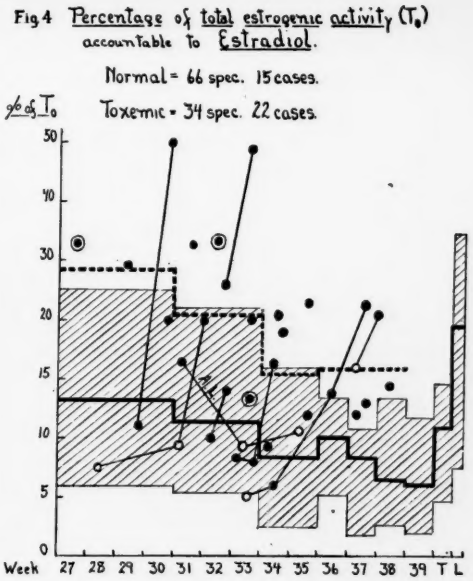

Fig. 4. Urinary estradiol in normal pregnancy, preeclampsia and eclampsia (percentage of total estrogenic activity).
For explanation of symbols, see figure 2.

than the actual amounts of this highly active compound excreted. In normal pregnancy, the percentage figures for estradiol, both in individual patients and composite curves, show decreasing values between the 28th and 38th weeks. Since estrone and estriol are increasing during this period, the drop in percentage of estradiol is taken as an indication of an increasing rate of conversion along with increasing production of estradiol. The actual values for urinary estradiol in toxemia fall above, below and within the normal range. Although many of the percentages are also within the normal range, it is apparent that in general the percentage of total estrogenic activity accountable to estradiol in the urines of patients with toxemia is well above normal. Furthermore, in the women from whom repeated specimens were obtained there is consistent evidence, with one exception (*Mrs. A.L.*, v.s.) for increasing rather than the normally decreasing percentage figures as pregnancy advanced. Considered in the light of reduced pregnandiol and estriol excretion, this finding would be interpreted as indicating a decreasing rate of estradiol to estrone conversion due to a failure in estrone to estriol conversion due, in turn, to a progestin deficiency.

Estrone (*fig. 5*). In the first paper of this series, it was pointed out that rapid destruction of estrogen is consistently accompanied by markedly reduced activity, both in percentage and weight, in the estrone fraction. In practically no urine from women showing clinical manifestations of preeclampsia or eclampsia have we been able by bioassay to detect any ketonic estrogen, i.e., estrone, whatsoever. This observation again is cogent evidence of progestin deficiency with consequent rapid destruction of estrogens. In 2 of the patients from whom urines were collected just prior to the appearance of toxic signs, unusually high values for estrone were found. In both, high estrone figures failed to be accompanied by high levels of estriol, indicating that we had caught the period when failure of estrone to estriol conversion had appeared and just before the onset of the rapid destruction which is so constant a finding as soon as toxic signs become evident. In *Mrs. A.L.* the spontaneous disappearance of toxic signs was accompanied by a reappearance of estrone, a token of decreasing destruction. Toxic signs, therefore, appear to be intimately associated with the stage of progestin deficiency at which rapid destruction of estrogens occurs.

T_{zn}:T_0 ratios (*fig. 6*). The increased estrogenic potency of the urine of women after zinc hydrolysis over that which may be acquired by simple acid hydrolysis has been shown to be largely accountable to the conversion of non-estrogenic constituents into estrogens (14). All of our evidence to date is in keeping with the assumption that rehydrogenation of oxidized estrogen breakdown products is involved and that T_{zn}:T_0 ratios may be taken as a gauge of estrogen destruction in the body. In 8 of the normal and 16 of the toxemic patients these ratios were determined. Preeclampsia and eclampsia are characterized by high ratios, thereby

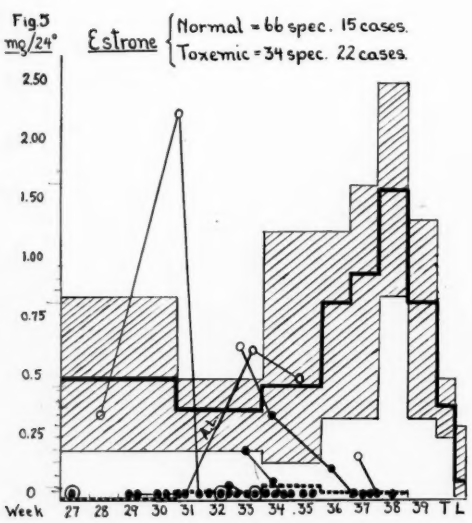

Fig. 5. Urinary estrone in normal pregnancy, preeclampsia and eclampsia (mg. per 24° volume).
For explanation of symbols, see figure 2.

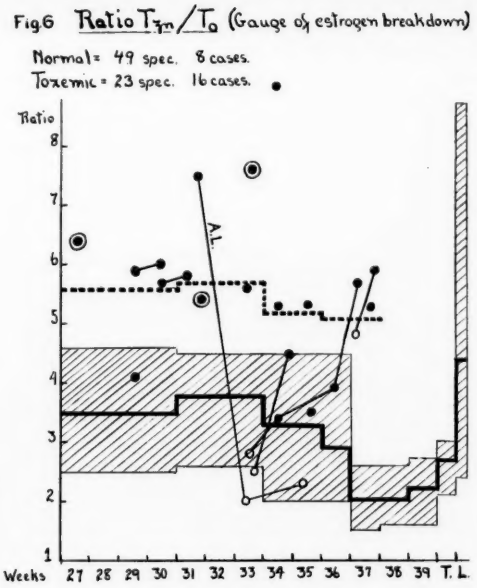

Fig. 6. Urinary $T_{zn}:T_0$ ratios (gauge of estrogen destruction) in normal pregnancy, preeclampsia and eclampsia.
For explanation of symbols, see figure 2.

completing the evidence for a progestin deficiency in these patients, accompanied by a resultant failure of estradiol to estrone to estriol conversion and their more rapid destruction. The marked drop in $T_{zn}:T_0$ ratios found in the urines of *Mrs. A.L.* when toxic signs disappeared as well as the rise in these ratios which accompanied the onset of clinical manifestations in the 3 cases studied prior to the onset of signs are of especial significance. All of the urinary findings on these 4 cases indicate a very close relationship between clinical manifestations and the rate of estrogen destruction.

DISCUSSION

In every pregnant individual followed, both normal and toxemic, the values for the 5 quantitative assays of each specimen reflected the same changes in estrogen and progestin metabolism. The variations in pregnandiol excretion have in general been less marked and less consistent than those of the various estrogens. A marked shift in estrogen metabolism, moreover, is not always accompanied by a commensurate shift in estriol excretion. The most reliable indications of a progestin-deficient metabolism of the estrogens in any particular urine are (*a*) a high percentage of total activity accountable to estradiol, (*b*) an extremely low percentage or absence of estrone and (*c*) a high $T_{zn}:T_0$ ratio. Unfortunately, space does not permit the charting of the clinical condition together with the urinary findings on each individual studied. In each case of late pregnancy toxemia, the clinical course of the disease was paralleled by hormonal changes in agreement with our hypothesis that the toxic manifestations of preeclampsia and eclampsia are preceded by a progressive progestin and estrogen deficiency, are closely allied to the resultant rapid destruction of the estrogens, and are possibly directly accountable to some toxic product resulting from such destruction.

Rapid destruction of the estrogens of the same order as that observed after the onset of toxic signs in late pregnancy toxemia was apparent during labor (see preceding paper of this series), the only difference being that labor lasts for a comparatively short time and terminates in emptying the uterus of what is accepted as the source of trouble in preeclampsia and eclampsia, namely, the products of conception. Albuminuria, hypertension and shock are frequently observed in long labors[5] and might be considered toxic manifestations.

The problem that presents itself is to find the rea-

[5] One of the normal individuals followed through to delivery (*R.C.* of the preceding paper) was in labor for 48 hours. During the last 8 hours, her specimens contained large traces of albumin and her blood pressure rose to 150/90. Immediately after delivery, she went into shock. Albumin has been measured in the catheter specimens from 16 consecutive patients with normal deliveries at the Boston Lying-in Hospital. None had had any albuminuria or other toxic signs before labor. In 10 of these specimens there were appreciable amounts of albumin, that is, between 15 and 218 mg.%. It does not seem that labor in itself would be sufficiently violent exercise to account for this finding.

son for the deranged metabolism of the placental hormones which our data have so consistently shown to be characteristic of toxemia and which corroborates other evidence implicating the placenta as the immediate final cause of the disease. Consideration of our data has led us to believe that many primary etiological backgrounds may result utlimately in disordered placental metabolism.

In those patients followed into toxemia, the very earliest indication of impending trouble has been an elevation of serum CG. This observation in itself implies a placental abnormality as being involved early in the course of the disease.

We have speculated that the rise in serum CG might reflect a failure of utilization of this factor for progestin production (1, 12, 17) and that, in the small percentage of preeclamptics and eclamptics in whom no detectable elevation of CG is present, decreased production, e.g., from placental damage by toxemia,[3] along with failure of utilization might pertain. On the other hand, overproduction of CG as a compensatory mechanism in those patients with elevated CG has not been ruled out. The physiological significance of the level of serum CG in pregnant women is still unknown, but in cases of toxemia it is apparent that whatever the rate of the placental elaboration of CG, this factor is not being normally utilized for steroid production.

Anterior pituitary deficiency comes to mind as a possible cause for this failure in utilization, since a pituitary synergist has been found essential for the balanced production of progestin and estrogen in animals to which CG is administered. A pituitary deficiency is readily conceivable in diabetics in whom toxemia has consistently been associated with high serum CG (16 cases), and theoretically might also result from vitamin lack.

Siddall (18) has pointed out a relationship between the geographic distribution of a dietary deficiency of the B complex and the incidence of pre-eclampsia. Others (19, 20, 21) have found that B_1 deficiency in animals leads to reduction of hypophyseal gonadotropic activity.

A valuable lead intimating many other possible causes for placental failure in steroid production was gained by the discovery, reported in the preceding paper of this series, that uterine contractions and the resultant embarrassment of placental circulation cause an immediate reduction in the supply of progestin and estrogen and the accompanying shift in the urinary distribution of estrogens indicative of progestin-deficient metabolism and rapid destruction. Any influence which restricted the blood supply to the placenta, or made it inadequate for the growing demands of the uterus and its contents, would be expected to have a similar effect. Numerous mechanical, functional and organic disturbances might affect adversely the functional integrity of the vascular supply to all or parts of the uterine contents, any one of which might be considered primarily responsible for a changed metabolism of placental steroids. An analogous situation is the change in renal metabolism and hypertension resulting from relative ischemia. Unless these disturbances were self-corrected or premature delivery occurred, toxic manifestations, if they are the result, as we believe, of this changed metabolism, would be expected to develop.

We are convinced that the significant finding, so far as the clinical manifestations of preeclampsia and eclampsia are concerned, is the sudden rapid destruction of estrogens. The menstrual phenomenon has also been found to be accompanied by the same evidence for rapid destruction of the estrogens following estrogen and progestin withdrawal (10, 14). Furthermore, there is a striking similarity between the local changes in the premenstrual endometrium and the generalized disturbances so characteristic of preeclampsia and eclampsia. The menstrual discharge has been found to contain a potent toxin (22, 23) to the action of which we would attribute the local changes resulting in menstruation. The formation of this toxin appears to be closely allied to rapid destruction of the estrogens. By analogy, we would postulate that the same shift of steroid metabolism in pregnancy results in the formation, on a larger scale, of a similar toxin, possibly in the decidua. The albuminuria of preeclampsia might be ascribed to the effect of such a toxin acting on kidney glomeruli, the hypertension to an actual Goldblatt phenomenon from renal arteriolar constriction due to this same toxin, and edema to an effect upon capillaries similar to that which takes place in the premenstrual endometrium.

Whether or not the pathological changes of toxemia may be ascribed to the action of some specific toxin, an important aspect of these changes is the circulatory deficiency which must, in itself, interfere with the vascular supply to the placenta. Thus, with the establishment of pathological changes there must be an inauguration of a vicious circle in which circulatory and hormonal changes are amplifiying one another.

Two methods of approach suggest themselves as means of cutting in upon this vicious circle in cases of severe preeclampsia and eclampsia. The first is to neutralize the hypothetical toxin and the second to prevent its further formation by re-establishing adequate blood supply to the placenta and replacing the progestin and estrogen deficiency. The more advanced the pathological and hormonal changes, the more difficult it would be to accomplish this second aim. Furthermore, if, as we have suggested, preeclampsia and eclampsia may have a number of etiological backgrounds all resulting in deranged placental metabo-

lism, directly or through uterine ischemia, it is obvious that some of these processes, e.g., cardiac decompensation, cannot be affected favorably by hormone administration and may in themselves make prevention or remedy of the metabolic change in the steroids impossible. The indications are that any attempts at hormone replacement must be made early in the course of the disease or as a preventive measure. Endometrial bleeding may be prevented by the administration of adequate amounts of estrogen or progestin. To determine conclusively whether the administration of these steroids would similarly prevent the development of toxemia of late pregnancy would necessitate extensive clinical trials and involve the use of very large amounts of these preparations. Suggestive results after hormone administration have been reported (2, 10, 24, 25) and further studies of a similar nature will be presented in the following paper.

SUMMARY

Elevated serum chorionic gonadotropin has been demonstrated in 84 of 100 cases of preeclampsia and eclampsia and in 8 of 13 premature deliveries. In 28 of the cases with toxemia and 7 of those delivering prematurely, analyses were performed at weekly intervals from early in pregnancy and an abnormal rise detected 4 to 8 weeks prior to these clinical episodes.

Pregnandiol, estriol, estradiol, estrone and the estrogenic potency after hydrogenation have been measured in the urines of 22 cases of preeclampsia and eclampsia and in specimens from 15 normal individuals during the last trimester. Low or decreasing pregnandiol and estriol, high or increasing percentage of estrogenic activity accountable to estradiol, decreasing or absent estrone and high or increasing ratios of estrogenic potency after hydrogenation characterized the urines of every toxemic case. These results indicate that this disease of late pregnancy is closely associated with a progressive deficiency of progestin, a concomitant decrease of estrogen and a consequent changed metabolism of estrogen involving greater and more rapid destruction.

The significance of these data in relation to etiology, prevention and treatment of toxemia of late pregnancy is discussed.

We acknowledge with gratitude the cooperation of Drs. Priscilla White, Robert L. DeNormandie, Weston Sewall, Duncan E. Reid, Samuel B. Kirkwood and Spencer C. Flo, and the technical assistance of Miss Sara Schiller.

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III. THE EFFECT OF HORMONE ADMINISTRATION IN PREECLAMPSIA[1]

ESTROGEN AND PROGESTIN METABOLISM IN PREGNANCY

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THE FINDING of a deficiency of progestin and estrogen in cases of preeclampsia and eclampsia has naturally led to attempts at replacement therapy. Such attempts have been conducted on a limited number of patients because of the fact that we were as much interested in the resultant hormonal effects as in the clinical outcome, and for this reason have insisted upon performing complete analyses[2] on repeated specimens of blood and urine before, during and, whenever possible, after hormone administration. These analyses, though laborious and time-consuming, are necessary adjuncts to an investigation in which the emphasis must still be as much upon the research as the clinical aspects of the problem. The primary object of these studies has been to learn more about hormonal interrelationships in late pregnancy toxemia and to obtain leads as to possible methods of preventing and alleviating the eclamptic syndrome.

In a previous communication (1) we reported the result of steroid injections in 6 women who, during the last trimester of pregnancy, were exhibiting the endocrine imbalance characteristic of preeclampsia. Four had mild, or grade 1, preeclampsia when hormone administration was begun, and 2 were treated, as a preventive measure, on the basis of the hormonal deficiency only. Although the results warranted no final conclusion as to the clinical value of such treatment, since control of the disease might have followed the usual management alone, there was evidence of a more normal metabolism of estrogen and progestin for the duration of steroid administration (8 to 44 days), and the close correlation between clinical and hormonal changes strongly suggested that the clinical manifestations were the direct result of some process associated with a progestin-deficient metabolism of the estrogens. It was demonstrated that a re-establishment of a more normal metabolism of the steroids by replacement therapy could be accomplished only by the injection of both estrogen and progestin, since an adequate amount of one appears to be required to prevent rapid destruction of the other.

These studies indicated that increased destruction of placental steroids characterized the stage of toxemia at which the first clinical signs appeared and was more pronounced when toxic signs became more severe. Even in these early mild cases, replacement therapy had no beneficial effect either upon the hormonal or the clinical picture until the daily injection of large amounts of estrogen and progesterone had been continued for 6 or more days. Compounds closely related to the placental steroids have been found to enhance their biological activity, presumably through protecting them against destruction (1, 2). An experiment was tried, therefore, in which the effect of supplementing estrogen and progestin injections with sodium pregnandiol glucuronidate orally was investigated.

Mrs. G. K., a severe diabetic, aged 18, had been followed by us through her first pregnancy, complicated by preeclampsia (1). During this, her second pregnancy, repeated analyses for serum chorionic gonadotropin (CG) revealed an abnormal rise starting at the 25th week and becoming more marked during the following 8 weeks, with no clinical signs of toxemia. During the 33rd week, gross edema (a gain of 9 lb. in 4 days), hypertension (160/90–110), severe headache and slight albuminuria developed. Complete urinalyses revealed that the onset of toxic manifestations was accompanied by the typical rapid increase in the rate of estrogen destruction. After 5 days of routine hospital care, the patient showed no clinical improvement other than the disappearance of visible edema. Daily injections for 7 days of 20 mg. of progesterone and 10 mg. of estradiol benzoate, together with 100 mg. of sodium pregnandiol glucuronidate by mouth, were accompanied by a drop in serum CG to normal levels and evidence in the

Received for publication March 12, 1941.

[1] The Mrs. William Lowell Putnam Investigation of the Toxemias of Pregnancy, aided by grants from the Committee for Research in Problems of Sex of the National Research Council.

[2] For methods, see the preceding papers of this series.

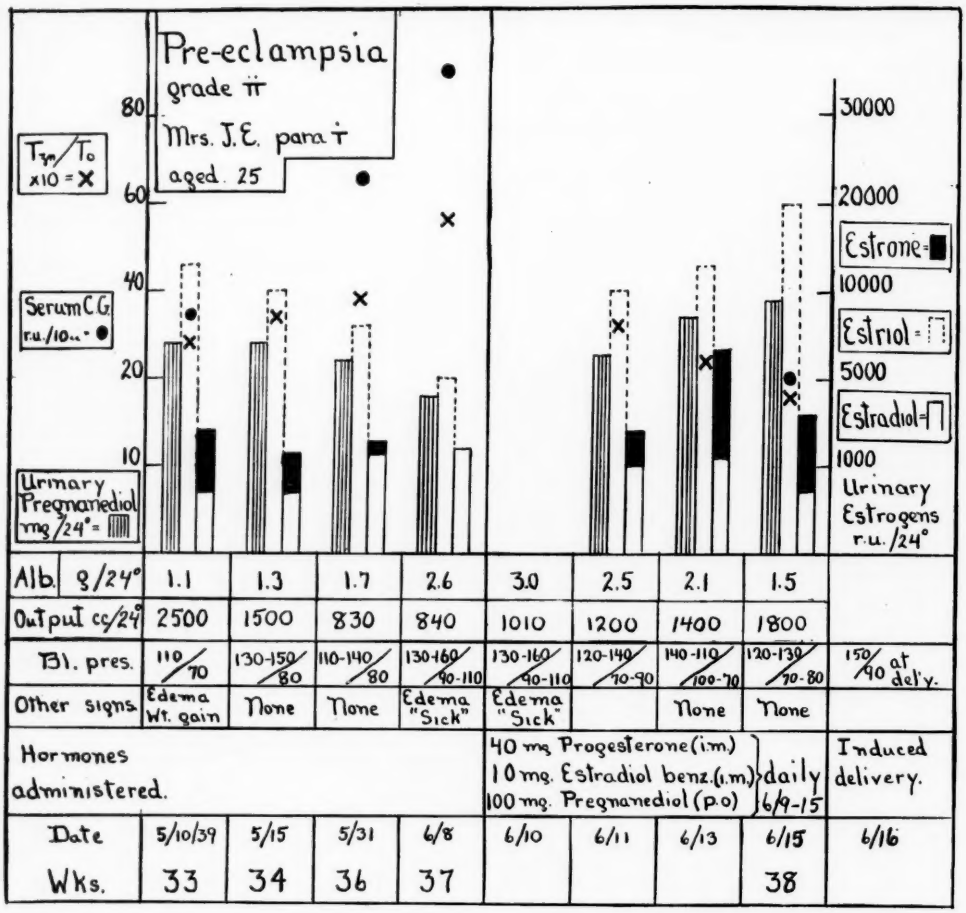
Pre-eclampsia
grade II
Mrs. J.E. para I
aged 25
T_m/T_o x10 = X
Serum C.G. r.u./10.. •
Urinary Pregnanediol mg/24° =
80
60
40
20
10
30000
20000
Estrone =
10000
Estriol =
5000
Estradiol =
1000
Urinary Estrogens r.u./24°
Alb. g/24° 1.1 1.3 1.7 2.6 3.0 2.5 2.1 1.5
Output cc/24° 2500 1500 830 840 1010 1200 1400 1800
Bl. pres. 110/70 130-150/80 110-140/80 130-160/90-110 130-160/90-110 120-140/70-90 140-110/100-70 120-130/70-80 150/90 at del'y.
Other signs Edema Wt. gain None None Edema "Sick" Edema "Sick" None None
Hormones administered. 40 mg. Progesterone (i.m.) 10 mg. Estradiol benz. (i.m.) 100 mg. Pregnanediol (p.o.) daily 6/9-15 Induced delivery.
Date 5/10/39 5/15 5/31 6/8 6/10 6/11 6/13 6/15 6/16
Wks. 33 34 36 37 38

Fig. 1. Effect of estradiol benzoate, progesterone and pregnandiol upon the hormonal imbalance of preeclampsia when started early in the course of the progressive deficiency of estrogen and progestin.

urinary findings for a steady increase, beginning 24 hours after the start of therapy, in the rate of conversion and decrease in the rate of destruction of estrogens. There was also a loss of weight, a drop in blood pressure and freedom from headache. For the following 5 days, when pregnandiol was omitted, the same daily dosages of estrogen and progestin were less effective, as demonstrated by urinary evidence for less complete conversion and more rapid destruction of the estrogens. After 7 more days of estrogen, progestin and pregnandiol, the clinical and hormonal condition of the patient was normal. Two days later, after the discontinuation of all hormone therapy, toxic signs reappeared together with urinary evidence for a progestin-deficient metabolism of the estrogens. An elective cesarean section was performed. Mother and baby did well.

The results on this patient led us to hope that pregnandiol might prove a valuable addition to estrogen and progestin in cases with more severe toxemia. Since our last publication, a total of 9 women (one diabetic, *Mrs. G. K.*, above) showing the clinical signs and symptoms of preeclampsia and the urinary findings indicative of rapid steroid destruction have been given intramuscular injections of 10 mg. of estradiol benzoate and 30 to 50 mg. of progesterone daily, together with sodium pregnandiol glucuronidate by mouth (100 or 200 mg. daily). All had more severe toxemia than the 6 previously reported cases (1). In only 2 of the 9 were clinical improvement and a more normal steroid metabolism maintained for the duration of injections. One of these was *Mrs. G. K.* (above) and the other *Mrs. J. E.*, the findings upon whom are presented in figure 1.

This patient was admitted when 33 weeks pregnant primarily because of excessive weight gain. She had mitral

and aortic insufficiency, which was considered responsible for the slight albuminuria and edema. Serum CG was found to be high. The urinary findings, except for low pregnandiol, were within the range of normal for this period of gestation. During the following 3 weeks, on routine hospital care, urinalyses showed that the estrogen and pregnandiol output as well as the rate of estradiol to estrone to estriol conversion were decreasing rather than undergoing the normal increase for this period of pregnancy and that the $T_{an}:T_0$ ratio was increasing slightly. There was also a steady increase in urinary albumin and a rise in systolic blood pressure, although the edema disappeared. During the 37th week, coincident with the disappearance of urinary estrone and a marked rise in $T_{an}:T_0$ ratio (evidence for rapid destruction of estrogen), toxic signs suddenly became more severe and the patient complained of drowsiness and dull headache. Hormone administration was instituted and within 48 hours there was evidence of hormonal and clinical benefit, which became more apparent during the 7 days that it was continued. By this time the patient was in the 38th week with a viable baby and a favorable cervix. Labor was induced by artificial rupture of the membranes. Mother and child did well.

The results on 7 other patients with severe preeclampsia to whom progesterone, estradiol benzoate and pregnandiol were given have been less encouraging. Although there was improvement, both clinical and hormonal, during the first few days of treatment, the continued administration of all 3 compounds in the same daily amounts was accompanied by a recrudescence before the seventh day of both the clinical and hormonal abnormality. The results presented in figures 2 and 3 are typical. None of these 7 patients had been studied by us prior to the onset of severe toxic signs, so that we have no means of knowing how long the progressive estrogen and progestin deficiency had been going on before the beginning of hormone treatment. Four of them (including *Mrs. M. H.*, fig. 2) had had toxemia clinically for 4 to 6 weeks before the period of study. In these 4 the levels of total urinary estrogens and pregnandiol were found to be extraordinarily low by the time the toxic condition became alarming. The other 3 patients of this group (including *Mrs. Tr.*, fig. 3) had severe fulminating preeclampsia. Toxic signs and symptoms had become alarming during the course of one week or less, no toxemia having been previously apparent. In these, also, urinary estrogens and pregnandiol were extremely low. It is possible that in such cases, in

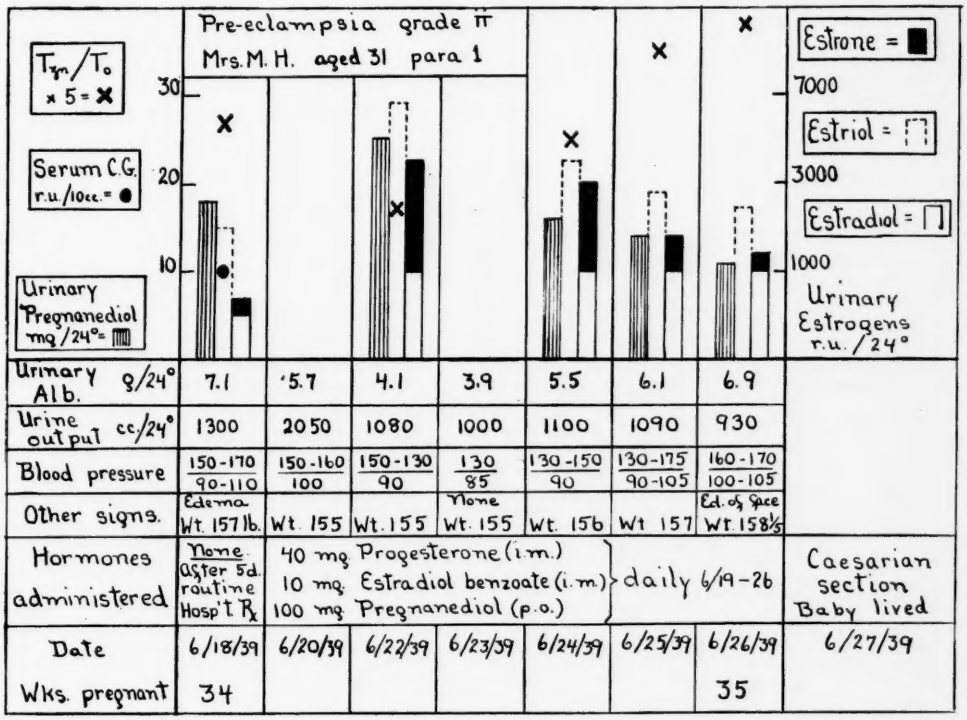
Pre-eclampsia grade III
Mrs. M. H. aged 31 para 1
Tan/To x 5 = X
Serum C.G. r.u./10cc. = ●
Urinary Pregnanediol mg/24° = ▥
30
20
10
Estrone = ■
Estriol = ⬚
Estradiol = ⊓
7000
3000
1000
Urinary Estrogens r.u./24°
Urinary Alb. g/24° 7.1 5.7 4.1 3.9 5.5 6.1 6.9
Urine output cc/24° 1300 2050 1080 1000 1100 1090 930
Blood pressure 150-170/90-110 150-160/100 150-130/90 130/85 130-150/90 130-175/90-105 160-170/100-105
Other signs. Edema Wt. 157 lb. Wt. 155 Wt. 155 None Wt. 155 Wt. 156 Wt 157 Ed. of face Wt. 158½
Hormones administered None after 5d. routine Hosp'l Rx
40 mg Progesterone (i.m.)
10 mg Estradiol benzoate (i.m.)
100 mg Pregnanediol (p.o.)
daily 6/19-26
Caesarian section Baby lived
Date 6/18/39 6/20/39 6/22/39 6/23/39 6/24/39 6/25/39 6/26/39 6/27/39
Wks. pregnant 34 35

Fig. 2. Effect of estradiol benzoate, progesterone and pregnandiol upon the hormonal imbalance of preeclampsia when started 4 to 6 weeks after the onset of toxic signs and when the progressive deficiency of estrogen and progestin is advanced.

which the hormonal deficiency is apparently extreme, very much larger doses would overcome the destructive mechanism. Such a course of treatment, however, is still entirely impractical and we have no assurance that it would be successful.

In the preceding paper of this series it was pointed out that the preeclamptic syndrome must, in itself, establish a vicious circle. The circulatory deficiency which typifies preeclampsia and eclampsia must embarrass the placental circulation as it does the circulation to other organs. We have seen that failure in placental circulation results in a decreased supply of estrogen and progestin with the accompanying increased rate of destruction. The greatly augmented destruction which has been noted once toxemia becomes clinically manifest, therefore, is readily understood as well as the difficulty of breaking in upon this vicious circle in those cases in which circulatory embarrassment, as evidenced by severe toxemia, is marked.

Adrenal Cortical Extract

Moon (3) has summarized evidence identifying the circulatory deficiency of eclampsia with that of shock and associating shock with adrenal cortical failure. Furthermore, the pathological findings in the eclamptic adrenal (4) are similar to those in the adrenals of animals during the last stage of the 'alarm reaction' as described by Selye (5), namely, a picture of cortical exhaustion. We have described a similar condition in rats after a lethal dose of menstrual toxin (6). In the preceding paper of this series we suggested that this

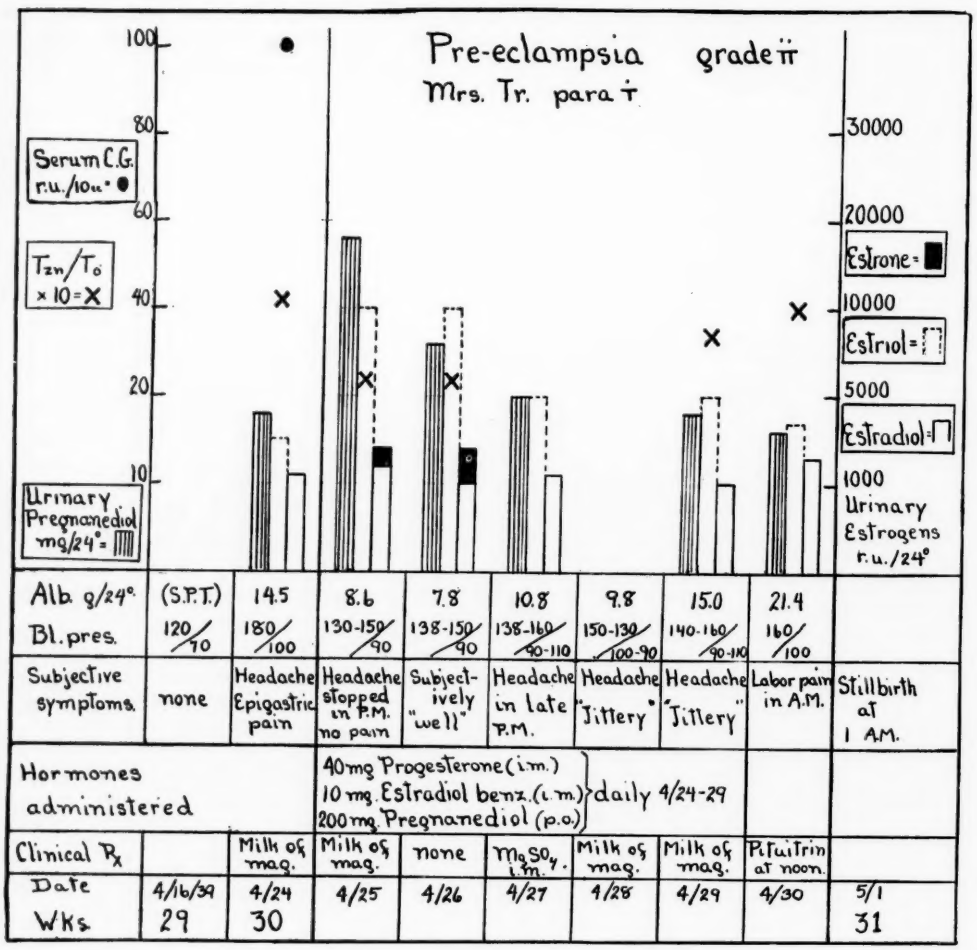

Fig. 3. Effect of estradiol benzoate, progesterone and pregnandiol upon the hormonal imbalance of fulminating preeclampsia.

same toxin, whose formation appears to be associated with rapid estrogen destruction, may be formed on a larger scale in preeclamptic and eclamptic patients. Shock may be combated, the final stages of the 'alarm reaction' prevented and the effect of menstrual toxin inhibited by adrenal cortical extract. It seemed possible, therefore, that adrenal cortical extract might aid in combating the circulatory embarrassment of severe preeclampsia and thereby the increased destruction of placental steroids which, in these patients, renders replacement therapy only temporarily effective. Figure 4 presents the results of such a therapeutic trial.

Mrs. H. H. was admitted when 34 weeks pregnant because of the sudden onset of a severe toxemic condition, namely, a gain in weight of 6½ lb. in one week, generalized edema, high blood pressure, a large trace of urinary albumin and severe headache. Except for mild headaches, she had been sign and symptom free one week before. After a week of routine hospital treatment, that is, rest, restricted water and salt, high protein diet and $MgSO_4$ catharsis, there was a loss of 5 lb. in weight, a reduction of the edema and headaches, but no effect upon blood pressure or albuminuria. Urinalyses gave evidence of a marked deficiency of estrogen and progestin with the accompanying rapid destruction of estrogens, as evidenced by absence of estrone and an extremely high $T_{sn}:T_0$ ratio. Seven days of hormone administration as shown on the chart was accompanied by 4 to 5 days of improvement in the clinical and hormonal condition, followed by a recrudescence of the hormonal and clinical abnormality in the face of continued administration. At this point, cortical extract[3] alone was subcutaneously administered for 4 days. The clinical effect was not spectacular, although there was a rather marked drop in urinary albumin, the subjective symptoms disappeared and the patient "felt" better. The effect on urinary estrogens was rather spectacular and quite unexpected. The marked rise in estriol and drop in $T_{sn}:T_0$ ratio, the decrease in percentage activity accountable to estradiol and the reappearance of estrone indicated an unmistakable increase in the rate of conversion and decrease in the rate of destruction of estrogens.[4] The membranes were artificially ruptured 3 days after the last injection. During these 3 days no hormone analyses were performed, but the urinary albumin rose steadily and gross edema and headache reappeared. The urinary findings during labor showed the typical depressant effect of uterine contractions on the supply of estrogen and progestin and the resultant rapid destruction. During labor, moreover, the toxemic condition became very much worse and the patient was in a state of coma for 6 to 8 hours. After delivery, mother and baby did well.

The findings in this patient have led us to speculate that adrenal cortical exhaustion may play a part in the alarming rapidity with which clinical manifestations may increase in severity in the preeclamptic patient. Up to a certain point, overactivity of the adrenal cortex may combat the 'toxin,' as in the first stages of the 'alarm reaction,' and also may aid in the prevention of its formation by increasing the rate of conversion and decreasing the rate of destruction of estrogens, thus partially replacing the progestin deficiency. The sudden increased severity of the disease and increased rate of estrogen destruction may perhaps both be accountable, at least in part, to adrenal exhaustion. On this basis, cortical extract might have therapeutic possibilities as a supplement to estrogen and progestin administration. In the experiment reported this was not investigated, since we first wished to discover the effect of cortical extract alone upon steroid metabolism.

Estrogen and Progestin Administration as a Preventive Measure

From the results thus far presented, it is apparent that the best chance of combating the progressive deficiency of estrogen and progestin which characterizes preeclampsia and eclampsia by replacement therapy depends upon beginning injections early in the course of the disease, before the circulatory embarrassment and the rate of steroid destruction become advanced. Urinary studies on 3 diabetics (2 have been reported (1)), to whom estrogen and progestin were given on the basis of a hormonal deficiency only, prior to the development of toxic signs, revealed a more normal metabolism of estrogen and progestin for as long as injections were continued (34 to 44 days). During hormone treatment mild toxic signs associated with evidence for increasing steroid destruction appeared sporadically but seemed to be controlled by increasing the dosages, suggesting that a more serious situation had been averted by the injection of barely adequate amounts of hormones (5 to 10 mg. of estradiol benzoate and 10 to 20 mg. of progesterone daily). The administration of estrogen and progestin as a preventive measure deserves further investigation, especially if less expensive preparations, effective orally, become available.

Unless complete urinalyses are performed before and during treatment, the results of such preventive measures are difficult to evaluate. We have seen that a progestin-deficient metabolism of the estrogens may

[3] Eschatin, Parke, Davis & Co., 20 cc. daily, equivalent to 500 dog units.

[4] This observation of the progestin-like effect of adrenal cortical extract upon estrogen metabolism has been checked. Injection of cortical extract in *Mrs. H.H.* during the postpartum period demonstrated that this material contains a factor which increases the rate of conversion and decreases the rate of destruction of the estrogens. Between the 6th and 18th days postpartum, three 72-hour urine specimens were collected and analyzed, one before, one during and one 5 days after the administration of 20 cc. of cortical extract daily for 3 days. Estrone was demonstrable only in the specimen collected during injections. This specimen also contained about 3 times as much estriol as the other 2; the percentage of total activity accountable to estradiol was 24, as compared with around 40 in the others; and the $T_{sn}:T_0$ ratio was only 1.5, as compared with 3.6 before and 3.2 after injections.

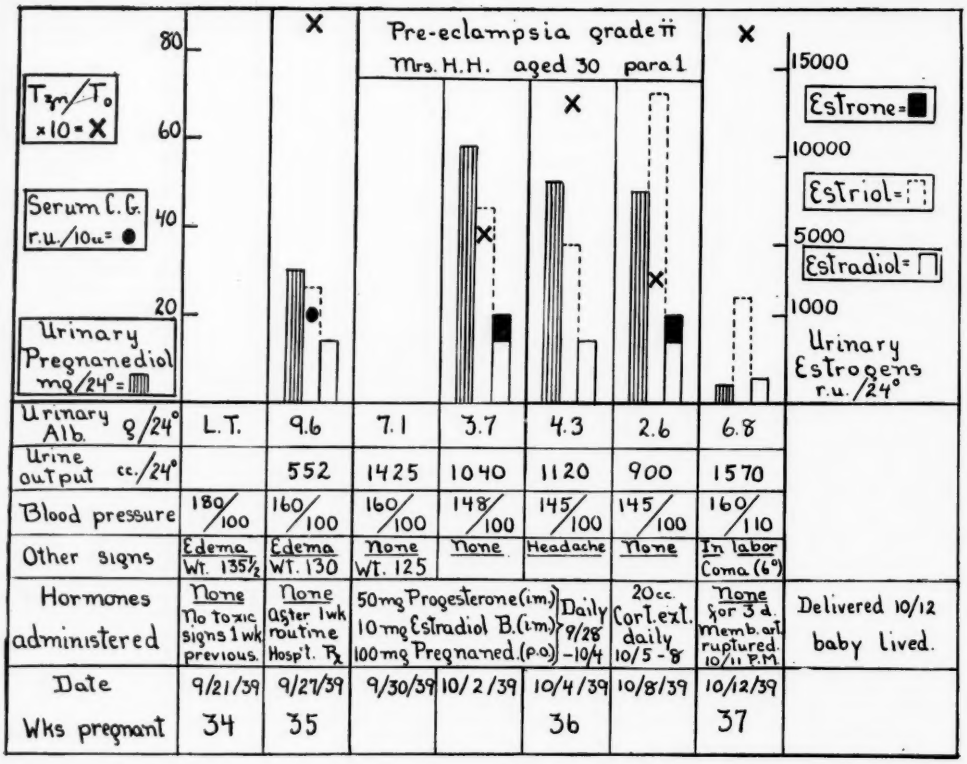
Pre-eclampsia grade II
Mrs. H.H. aged 30 para 1
80
60
40
20
Tm/To ×10=X
Serum C.G. r.u./10u=●
Urinary Pregnanediol mg/24°=▥
15000
10000
5000
1000
Estrone=■
Estriol=⬚
Estradiol=□
Urinary Estrogens r.u./24°
Urinary Alb. g/24° | L.T. | 9.6 | 7.1 | 3.7 | 4.3 | 2.6 | 6.8
Urine output cc./24° | | 552 | 1425 | 1040 | 1120 | 900 | 1570
Blood pressure | 180/100 | 160/100 | 160/100 | 148/100 | 145/100 | 145/100 | 160/110
Other signs | Edema Wt. 135½ | Edema Wt. 130 | None Wt. 125 | None | Headache | None | In labor Coma (6°)
Hormones administered | None No toxic signs 1 wk previous. | None after 1 wk routine Hosp't. Rx | 50 mg Progesterone (i.m.) 10 mg Estradiol B. (i.m.) 100 mg Pregnanediol (p.o.) | Daily 9/28 -10/4 | 20 cc. Cort. ext. daily 10/5 - 8 | None for 3 d. Memb. ar ruptured. 10/11 P.M. | Delivered 10/12 baby lived.
Date | 9/21/39 | 9/27/39 | 9/30/39 | 10/2/39 | 10/4/39 | 10/8/39 | 10/12/39
Wks pregnant | 34 | 35 | | | 36 | | 37

Fig. 4. Effect of adrenal cortical extract upon the hormonal imbalance of preeclampsia at the time when parenterally introduced sex steroids are proving ineffective because of their rapid destruction.

be self-corrected (*Mrs. A. L.* of the preceding paper). Sufficient study was made of the 16 cases thus far treated under our supervision (3 prior to the development of toxic signs) to warrant the assumption that a progressive hormonal imbalance which would not have been self-corrected pertained. Of the 9 patients in whom there was evidence for continued clinical and hormonal benefit, 7 were diabetic. We believe the reason for this lies not in the fact that they were diabetic but because treatment was started early.

Having discovered, from our studies in pregnant diabetics (1, 7, 8), that the hormonal imbalance typical of preeclampsia seemed to be associated, in these women, not only with toxic signs but also with instances of premature delivery and fetal death, we persuaded Drs. Priscilla White, Elliott P. Joslin and Raymond S. Titus, who were concerned over the high fetal mortality in diabetics, to let us try the effect of early treatment in 9 of their patients in whom our studies had revealed evidence for this progressive endocrine abnormality. These were the first 9 therapeutic trials with estrogen and progestin at the New England Deaconess Hospital, the clinical results of which were reported independently in 1939 by Dr. White, et al. (9). Our study of estrogen and progestin metabolism in 5 of these was covered in our 1940 publication (1). The results were hopeful and the New England Deaconess Hospital group has continued independently with this form of preventive therapy on a larger scale. The results continue to be promising (10) but inasmuch as complete urinalyses on a large number of cases is impossible in a clinical laboratory, Dr. White, et al., have had to depend upon the levels of serum CG and urinary pregnandiol as an index of the endocrine balance of each patient before and during treatment. From our own studies we have come to realize that the quantification of these 2 factors alone cannot be relied upon to provide a true index of estrogen and progestin metabolism. The hormonal effect of orally administered synthetic estrogen and progestin has yet to be demonstrated, since in none of such trials have complete urinalyses been performed. Although the early administration of steroids offers promise as a practical therapeutic measure in diabetic pregnancies, clinical benefit can be justly evaluated only after the accumulation of a sufficient number of treated cases, together with a similar number of untreated controls in whom high serum CG has been detected, to permit unequivocal conclusions.

DISCUSSION

The therapeutic limitations of estrogen and progestin in preeclampsia are indicated by the results

presented. In the amounts thus far administered, these hormones, unless given early in the course of the disease, may be expected to have no more than a temporary palliative effect. Even temporary alleviation, however, is of considerable importance in a severe preeclamptic in whom the possibility of postponing the termination of pregnancy for as little as one week may make the difference between a viable and a non-viable infant. The indications are that even in those cases in which injections were started early the amounts of estrogen and progestin were barely adequate to prevent the rapid destruction of steroids that is consistently associated with steroid deficiency and to control the clinical manifestations for the duration of treatment. The difficulty and expense of the daily injections of adequate quantities of these preparations over prolonged periods stands in the way of extensive clinical trials. From the therapeutic angle, therefore, our studies as yet offer little that may be considered of practical value to the clinician.

From these studies, however, we have gained our most persuasive evidence that steroid deficiency and the resultant change in estrogen and progestin metabolism is causally related to the clinical manifestations of preeclampsia. Ten of the 13 patients treated after the onset of toxemia had had at least 5 days of routine hospital care (bed rest, $MgSO_4$ catharsis, water and salt restriction and high protein diet) before injections were started, in spite of which the clinical and hormonal condition was becoming progressively more alarming until estrogen and progestin were given. Furthermore, in each of 6 cases in whom hormone administration was discontinued prior to the termination of pregnancy, there was an unmistakable recrudescence of the clinical and hormonal abnormality within a few days after the last injection. Thus, since we have demonstrated that estrogen and progestin administration can shift the hormonal and clinical changes in the direction of normal, it is logical to assume that both the hormonal and clinical abnormality result from estrogen and progestin deficiency.

The observed progestin-like action of cortical extract upon estrogen metabolism carries a number of theoretical implications of general interest. (*a*) A reciprocal relationship between progestin and the adrenal cortex is suggested, since progestin has been found to prolong the life of adrenalectomized animals (12). (*b*) The fact that cortical extract prevents estrogen destruction is of significance in connection with the observation that estrogens are highly toxic to adrenalectomized animals (12, 13). It is possible that the toxic factor, in this situation, is some compound formed as a result of estrogen destruction. (*c*) That adrenal cortical extract and testosterone (1) both simulate progestin in their effect upon estrogen metabolism may explain why a certain amount of estradiol to estrone to estriol conversion has been observed in the absence of any progestin (14, 15, and unpublished observations by the authors). In the normal menstrual cycle and in pregnancy, however, the partition of these urinary estrogens appears to provide a reliable gauge of progestin activity (1, 11, 16).

SUMMARY

The effect of estrogen and progestin administration upon the hormonal abnormality of preeclampsia has been investigated in a total of 16 cases to January, 1941. Nine were severe preeclamptics at the start of injections, 4 were mild, and 3 were treated prophylactically on the basis of findings indicating the progressive steroid deficiency which precedes toxic manifestations.

Pregnandiol by mouth enhances the beneficial effect of steroid administration upon estrogen and progestin metabolism. In the 9 severe preeclamptics, injection of the steroids was supplemented by sodium pregnandiol glucuronidate orally.

There was evidence for clinical and hormonal improvement for the duration of treatment (7 to 40 days) in the 4 mild and in 2 of the severe preeclamptics. In 7 of the severe cases, temporary clinical and hormonal benefit was followed by a recrudescence of both abnormalities before the seventh day of continued injections.

Adrenal cortical extract contains a factor capable of replacing progestin in the conversion of estrogens and in their protection against destruction.

In the 3 patients to whom estrogen and progestin were administered as a preventive measure, the mild toxic signs and evidence for increased rate of estrogen destruction which developed despite injections appeared to be controlled for the duration of treatment (34 to 44 days) by increasing the dosages of administered hormones.

The therapeutic limitations of estrogen and progestin administration in preeclampsia are discussed, as well as the difficulty of evaluating clinical benefit under those conditions in which results have been most promising, i.e., when injections are started early in the course of the progressive hormonal and circulatory deficiency.

The close correlation between the clinical and hormonal findings and the fact that both abnormalities may be alleviated by estrogen and progestin administration (even though only temporarily in the severe preeclamptics) has led us to the conclusion that the clinical manifestations of preeclampsia are the direct result of a changed metabolism of the sex steroids involving a greatly increased rate of destruction and accountable to estrogen and progestin deficiency.

We are indebted to Drs. Robert L. DeNormandie, Frederick C. Irving, Samuel B. Kirkwood, Duncan E. Reid, Weston Sewall, Raymond S. Titus, Roy R. Wheeler and Priscilla White for their cooperation and to Miss Sara Schiller for technical assistance.

We acknowledge with gratitude generous supplies of estradiol benzoate (Progynon-B) and progesterone (Proluton) from the Schering Corporation.

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I. EFFECT OF PROGESTERONE AND THE GONADOTROPIC HORMONE OF MARE'S SERUM ON THE EXCRETION OF ESTROGENS, ANDROGENS AND SODIUM PREGNANDIOL GLUCURONIDATE BY WOMEN DURING NORMAL AND ABNORMAL MENSTRUAL CYCLES[1,2]

HORMONE THERAPY AND SEX HORMONE EXCRETION

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A NUMBER OF WORKERS have studied the influence of the injection of a pure hormone on the output of its excretion product. The output of injected estrone has been variously reported as from 3 to 20% (1–5). All workers agree that a large proportion of this compound disappears in the body. This also seems to be true of the androgens (6–9). Progesterone does not appear to any considerable extent as such in the urine, even after the injection of relatively large doses, but Venning (10) has reported that sodium pregnandiol glucuronidate only appears in the urine during the luteal phase, and if progesterone is injected, the output of the pregnandiol complex is increased equivalent to as much as 60% of the injected progesterone. Buxton (11) has confirmed this when progesterone is injected into men, but Hamblen and coworkers (12–15) were unable to find increased pregnandiol output in women after similar treatment.

Much of the work in this field is open to the criticism that the daily fluctuations of endogenous hormone were not properly considered in determining the base from which to estimate the excess recovery. This is particularly serious when the excretion of administered estrogens has been studied in normal women. Work such as that of Koch and coworkers (16), Gustavson (17), Smith and Smith (18, 19) and Yerby (20) indicates that there are wide daily fluctuations in excretion from endogenous sources. Ovariectomized women and eunuchs do not have such wide endogenous variations. The effect of hormones injected into such individuals is not necessarily the same as in normal subjects.

Another factor that has not been considered in most studies is the influence of the administered hormone on other hormone fractions than that commonly accepted as the particular excretion product. It is natural that attention should be centered on the latter fraction when the primary interest is the percentage of recovery, but one must not forget the possibility of interconversion. And in evaluating therapeutic influence the effect on other hormones must be definitely considered. Hoskins, et al. (6), Dorfman (21) and Steinach and Kun (22) made such studies on the influence of testosterone on estrogen and androgen fractions, but did not determine the effect on the output of pregnandiol. Browne and Venning (23, 24, 25) and Hamblen et al. (26) have studied the influence of sex hormones and of gonadotropic extracts on pregnandiol output, but have not followed estrogens. Salmon (27) investigated the effect of testosterone propionate on the gonadotropin output of a castrate woman but did not follow the excretion of other factors.

Received for publication February 3, 1941.
[1] Supported in part by a Grant from the Graduate Medical Research Fund.
[2] Assistance in the preparation of these materials was furnished by the personnel of the Works Projects Administration, Official Project No. 165-1-71-124-(3), Sub-project No. 343.

The purpose of the present series of investigations is to determine the influence of the administration of various hormones on the simultaneous output of the different sex hormone excretion products. The studies include both normal women and those showing various types of chronic pathology. In order to do this it has been necessary to study the daily excretion of the various fractions in each individual for two or more menstrual periods to determine the basic cycle and its normal variations. This report covers the first series of investigations of this type after the administration of two hormone preparations: progesterone in oil and an aqueous solution of the gonadotropic hormone of pregnant mares' serum.

METHODS

The subjects selected for this study were individuals whose menstrual history for some time past was accurately known to the clinical investigator. Pelvic measurements, pelvic examinations, basal metabolic rate determinations and x-rays of the sella turcica were made on all subjects. Cooperation of the individuals under study was excellent in nearly all cases.

Since there was a wide variation in urinary excretion from day to day, samples were obtained daily from each subject over periods of 2 to 8 menstrual periods. Specimens were collected for the 12 hours from 7 P.M. to 7 A.M. since it has been demonstrated by a number of workers that the excretion of hormones is uniform over the 24-hour period within the limits of experimental error. Specific gravities were determined on each sample. Any in which the volume did not check reasonably with the specific gravity were investigated further. Only a few such samples were found. Two 12-hour specimens were combined and half the volume was taken for determination of androgens and estrogens. The other half was preserved with sodium cyanide and placed in a refrigerator for subsequent determination of sodium pregnandiol glucuronidate. The next pair of 12-hour specimens were combined in like manner and again divided into two parts, and one-half was used for the next determination of estrogens and androgens. The other half was combined with the half sample preserved from the previous pair and the whole analyzed for sodium pregnandiol glucuronidate. By this procedure we obtained a mean value for estrogens and androgens for each 2-day period and the average sodium pregnandiol glucuronidate excretion for every 4 days. The estrogen-androgen sample represented one-fourth of every 48-hour output while the pregnandiol samples represented one-fourth of every 96-hour excretion.

The hormone excretion during at least one menstrual period was followed before any hormone was injected. After a control record was obtained, a time was selected during the next menstrual period at which it was felt that a significant change in excretion might be recognized and a single dose of the hormone was given at this point. The excretion was followed throughout this menstrual period and in most cases for one menstrual period following that in which the injection was made.

The substances injected were progesterone in oil,[3] and gonadotropic hormone of mare's serum.[4] Doses ordinarily used were 10 mg. of progesterone and 30 Corner units of the gonadotropic hormone. These were enough to produce symptomatic disturbance in the normal subjects. In one individual a series of smaller doses of progesterone was given instead of a single large one.

Urine samples were extracted and separated into androgenic and estrogenic fractions by the method of Gallagher et al. (16).

Estrogenic assays were carried out by a modification of the technic described by Gustavson (17). The estrogenic fraction was evaporated to dryness and suspended in 25 cc. of water with the aid of glycol stearate. The suspension was then injected into spayed mice in 3 equal doses of 0.05 to 0.3 cc. at 8:00 A.M., 12:00 noon and 4:00 P.M. At first the vaginal smears were examined on the succeeding evening, 3 times on the second day and once on the morning of the third day following the injections. It was found, however, that the maximum reaction was always reached at some time on the second day so smears were only run 3 times on that day thereafter. Fifteen mice were injected with each dosage of an unknown sample. At least two doses of a standard solution of estrone were injected into similar groups at the same time. The amount of estrone which would be equivalent to the unknowns on the basis of the percentage of mice in estrus was then computed from the curve determined by the reactions of the groups injected with the standards. The accuracy and sensitivity of the method is attested by the fact that in parallel assays only once did 0.045γ of estrone give a reaction as strong as 0.06γ or 0.03γ give as high a percentage as 0.045γ. The total dose producing estrus in 50% of the mice usually lay between 0.045 and 0.06γ. The recoveries of estrone added to normal urines before hydrolysis on four different occasions ranged from 78 to 93%.

The polycyclic ketones in the androgen fraction were determined in the main by Friedgood's modification of Callow's method (28). Biological assays according to the 5-day capon method of Gallagher

[3] Supplied as Proluton by the Schering Corporation, Bloomfield, N. J.

[4] Supplied as Gonadogen by the Upjohn Company, Kalamazoo, Mich.

and Koch (29) were used to check certain samples.

Sodium pregnandiol glucuronidate analyses were carried out by the method of Venning (30) and a number were checked by the estimation of glucuronic acid. It was found that the determination of glucuronic acid was quite important with the small amounts of precipitates with which we were dealing. These often contained considerable amounts of impurities. The detailed method of glucuronic acid determination is to be published elsewhere. Briefly, the conjugated glucuronic acid was set free by hydrolysis with hydrochloric acid for 2.5 hours under 15 lb. steam pressure. It was then determined by the Somogyi modification of the Shaffer-Hartman method for reducing carbohydrates (31). On several occasions precipitates were obtained at times other than the latter third of the cycle. In all cases except one these did not yield significant amounts of glucuronic acid on hydrolysis. The apparent irregularities in excretion of sodium pregnandiol glucuronidate by normal women which have been reported by some workers (32) may have been due to a similar precipitation of impurities.

As has been pointed out by Venning, considerable losses occur when separating small amounts of this material. The loss appears to be largely due to solubility and is therefore more nearly a constant absolute amount than a constant percentage of the amount recovered. Since no correction for this loss has been made in our data, the values must be looked upon as relative rather than absolute.

RESULTS

Normal controls. Two normal young women were each studied for 3 or more menstrual periods. Each showed a healthy gynecoid pelvis, normal sella turcica, and normal basal metabolism. In each case there were known records of regular menstrual cycles for more than one year (fig. 1).

As in Gustavson's studies (17) there were two peaks, one appearing during the first half of the cycle at about the time of ovulation, and the other during the luteal phase. The findings differ from Gustavson's in showing a more regular occurrence of the peaks with reference to the menses, and in a more continuous excretion of estrogenic substances during the cycle. Since our samples were each a composite of 48 hours excretion, absence of hormone on a single day would have been missed. At no time was there a period of more than two days in which estrogens were not excreted.

The curves which we obtained resemble the type

TABLE 1. EXCRETION OF ESTROGENS AND ANDROGENS

Patient and treatment	Date beginning of period	Estrogens		Androgens, mg. eq. androsterone
		First cycle	Second cycle	
		I.U.	I.U.	
E. A. Control	11- 4-38	632	533	260
Control	12- 1-38	826	653	299
Control	12-27-38	659	747	293
Control	10-12-39	1030	1068	
10 mg. progesterone 11-28-39	11-10-39	1002	1241	308
Control	2-26-40		771	305
30 U gonadogen 4-12-40	3-22-40	1247	582	380
R. B. Control	11- 9-38	621	524	
Control	12- 6-38	586	704	
Control	1- 3-39	922		
Control	1-18-40	690	834	366
10 mg. progesterone 2-29-40	2-15-40	691	766	343
M. W. Control	2- 8-38	1096	1008	649
E. H. Control	2-13-38	1053	720	396
10 mg. progesterone 1-20-40	1- 6-40		662	318
10 mg. progesterone 2-18-40	2- 5-40	723	617	298
M. H. Control	10-13-39	933	683	290
1 mg. progesterone 11-27-39 to 12-8-39	11-12-39	879	953	390
E. Z. Control	11- 7-39 approx.	912	986	636
30 U gonadogen 2-7-40	2- 3-40	996	639	654

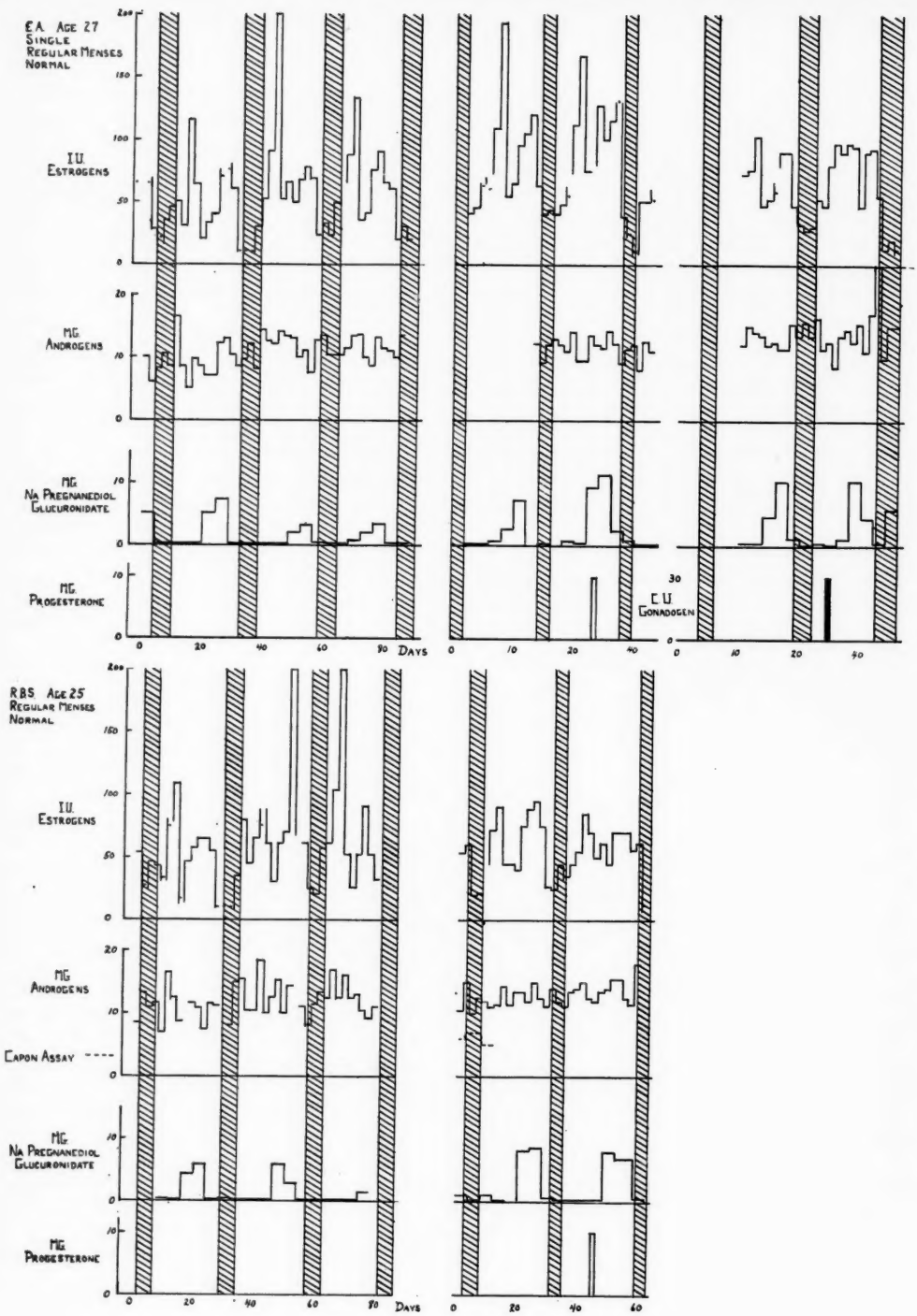

Fig. 1. NORMAL MENSTRUAL CYCLE. Shaded areas indicate menstruation.

of curve reported by Smith, Smith and Pincus (19) using colorimetric methods. The first peak appeared on the 11th to 15th day of the menstrual period and in most cases was sharper than the later maximum. The highest yields were rarely recovered in more than two of our 48-hour samples at this time, and often in only one. When the peak was limited to one it was usually greater than when the peak was spread over two samples, apparently because the sharp rise was so spaced with relation to the collection of our specimens on certain occasions that part appeared in the last of one 48-hour sample and part in the first of the next. Because of its abruptness, it has been thought that the first rise might be due to the escape of follicular fluid during ovulation. It often appeared earlier in the present cases, however, than ovulation is ordinarily supposed to occur. The sharp initial rise may be due simply to rapid secretion from the intact follicle.

The subsequent period of low excretion was apparently related to the period of the corpus hemorrhagicum when the secretory cells which form the corpus luteum are just beginning to proliferate. The second rise was usually a more prolonged one, with the maximum level ordinarily less than that reached during the first peak. This second maximum appeared to be associated with the function of the corpus luteum since it was correlated with the excretion of sodium pregnandiol glucuronidate.

While the form of the curve during the second cycle differed from that of the first, the total amount of estrogenic activity was approximately the same in both (table 1). In these computations the first cycle is taken from the beginning of menstruation to the low point after the first peak, and the second from this point to the beginning of the next menses.

The resemblance of the curves of excretion after lapses of 6 months or a year to those originally obtained, as well as the resemblance of consecutive cycles, indicates that the processes which cause these variations repeat themselves with relative uniformity in such normal subjects.

The absolute levels of estrogen in these studies are about one-fourth of that found by Gallagher et al. (16) using a rat assay. This is apparently because, as shown by Smith and Smith (33), the estrogens excreted are not all estrone. Using our assay technic in rats, the urinary estrogens were 3 to 5 times as active compared with estrone as when compared with the same compound in mice. Thus a level of 100 I.U. in our charts would be equivalent to 300 to 500 I.U. if measured in rats. This would give excretion values similar to those found by workers using a rat assay.

The ketosteroids of the androgen fraction, as determined by the Friedgood-Callow modification of the Zimmerman reaction, were equivalent to 10 to 15 mg. of androsterone, only occasional samples being far out of this range. No characteristic cycle could be identified. The capon assays gave a lower androgen equivalent than the chemical method (34, 35). The ratio between the two was not constant. This difference might be expected since dehydroandrosterone, biologically less active but chemically slightly more than equivalent, makes up a significant and probably variable proportion of the urinary androgens. In addition there are probably small amounts of biologically inactive compounds which give the chemical reaction (35).

In agreement with Venning (36), we have found sodium pregnandiol glucuronidate only during the second half of the menstrual cycle in normal women who had not received hormone injections. Precipitates of 0.6 mg. or less were considered negative. When larger precipitates were obtained at other times of the cycle they failed to yield glucuronic acid. These occurred only three times in the entire series of analyses. The excretion of the salt in the normal subjects varied between 26.7 mg. and 68.9 mg. per menstrual period (av. 42.2 mg.). As pointed out under "methods," this did not represent the absolute amount excreted, but only the recoveries under standard conditions. When dealing with precipitates of the size recovered here, considerable losses occurred, and these were relatively larger in the smaller precipitates.

Sterility cycles. The two individuals studied had normal menstrual cycles, and normal anatomical findings. They were both sterile, however; in fact it was this complaint which brought one of these women to our attention. Patient *E. H.* also complained of premenstrual edema. In *case M. H.* an endometrial biopsy was obtained during the latter part of a previous menstrual cycle and this was reported to show a secretory structure.

In both, the estrogenic assays showed only the first or ovulatory peak (fig. 2). This first peak showed the abrupt rise characteristic of the normal individual, and a maximum level within the normal range. All indications are that this represents either development to the point of ovulation or ovulation itself. Subject *M. H.* also showed the abrupt drop seen in normal women. In the other subject, *E. H.*, the drop which followed the first peak differed from the normal in that the estrogenic activity tapered away during the balance of the second half of the period. This would be the sort of curve one might expect from a follicle undergoing atrophy.

The absence of the second rise was associated in both cases with recovery of only small amounts of sodium pregnandiol glucuronidate from the urine.

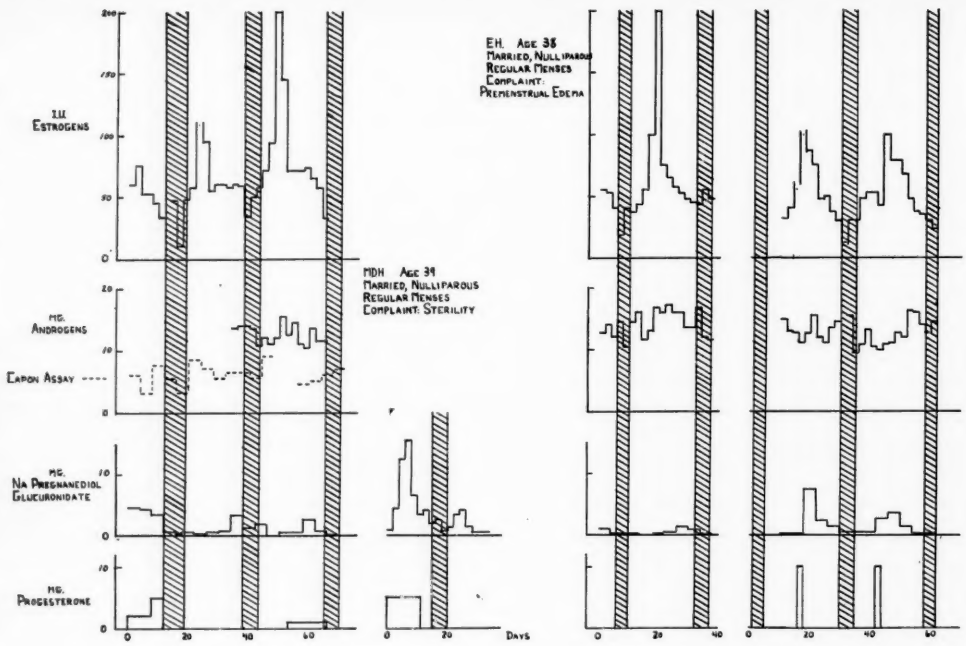

Fig. 2. Menstrual cycles with single estrogen peaks. Shaded areas indicate menstruation.

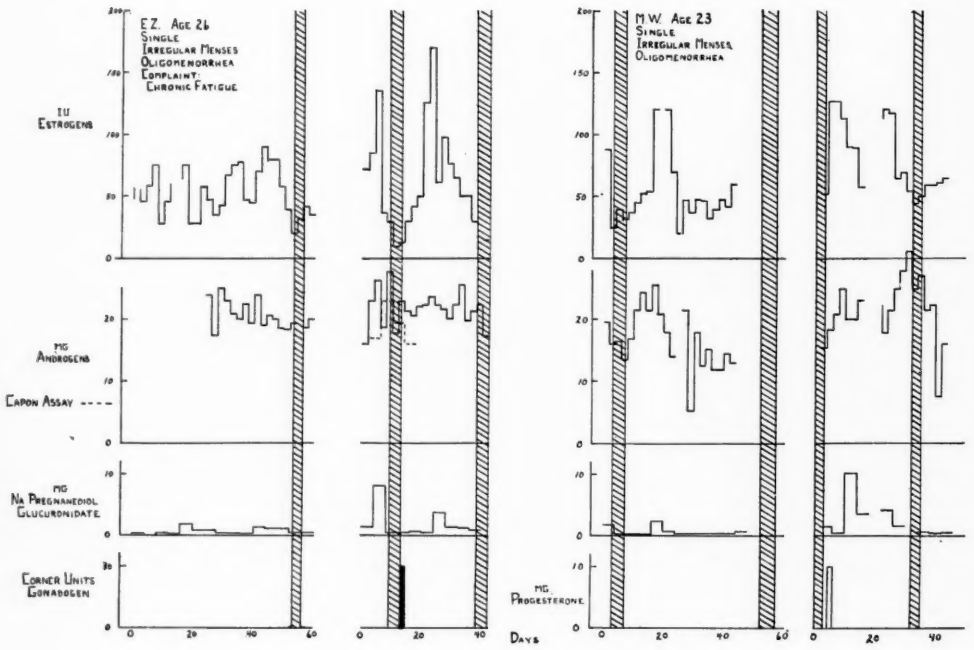

Fig. 3. Menstrual cycles with high androgen excretion. Shaded areas indicate menstruation.

TABLE 2. EXCRETION OF INJECTED PROGESTERONE AS SODIUM PREGNANDIOL GLUCURONIDATE

Subject	Av. sod. preg. glucuronidate output without injection	Progesterone injections	Total progesterone injected	Sod. preg. glucuronidate output after injection	Increase	
					Equiv. progesterone above av. control period	Equiv. progesterone above highest control period
	mg.	*mg.*	*mg.*	*mg.*	*mg.*	*mg.*
E.A.	39.6	1×10	10	97.9	36.0	27.7
R.B.	54.1	1×10	10	88.1	21.0	6.9
E.H.	26.8	1×10	10	49.3	13.9	5.6
M.H.	32.6	8× 1 1× 2 2× 4	18	57.2	15.2	12.3
	32.6	11× 5	55	110.0	68.0	65.1
	32.6	12× 1	12	37.2	2.8	−0.1

It would seem, therefore, that the second rise in estrogen excretion depended upon a functioning corpus luteum.

Cycles with high androgen levels. In two cases the greatest abnormality in the assays was the high level of ketosteroids in the androgen fraction (fig. 3, table 1). In these the values lay between 15 and 30 mg. per 24-hour period or a total excretion of more than 600 mg. for a period compared with 260 to 380 mg. for the normal subjects. This increase was mainly in biologically active androgens since capon assays show about the same absolute difference from the colorimetric values which was seen in normal individuals. Both of these cases suffered from oligomenorrhea and irregular menses. Anatomical measurements were normal but the B.M.R. in both was low. Each also showed psychological disturbances, but there was no obvious masculinity either psychologically or physically.

Case E. Z. had normal estrogenic cycles although in one month there was no menstruation. Except for one menstrual period, the output of sodium pregnandiol glucuronidate was normal.

Case M. W. also had double-peaked estrogenic cycles between menstruations. The output of sodium pregnandiol glucuronidate appeared at the proper times in relation to the menses although the amounts were below the normal average. The effect of the increased output of androgens appeared, therefore, to be antagonistic to the action of the ovarian hormones on the uterus, an influence observed in experimental animals (37, 38). Mazer and Mazer (39) have used testosterone to stop dysfunctional uterine bleeding in women, while Papanicolaou, Ripley and Schorr (40) have used it to inhibit menstruation. It seems, therefore, that the higher androgen level could account for the oligomenorrhea.

If the increased androgens had caused pituitary depression as postulated by these workers, one would have expected a decreased output of estrogens and progesterone. This was certainly not true of the estrogens and probably not true of progesterone. A direct inhibition of the uterus by the androgens seems therefore more probable than pituitary depression.

Since the estrogenic fraction in all of our cases represented only a small proportion of the sex hormone excretion, the total output of gonadal hormones was practically doubled in cases *E.Z.* and *M.W.* This must have been due either to a decreased destruction or an increased production. The normal estrogen excretion indicates that any increased destruction would be specific for androgens. The more probable explanation is that of increased production. The normal estrogen excretion also indicates that the excess androgen was probably formed in tissues which did not produce estrogens. The adrenal might possibly have been at fault.

Injection of progesterone. Table 2 shows the amount of pregnandiol recovered after progesterone injections, in excess of the average output of each subject during the untreated cycles. In every case a considerable proportion of the injected progesterone was recovered even when compared with the highest previous cycles. These results confirm the findings of Venning (10) and Buxton (11), and indicate that injected progesterone is probably metabolized in the same way, and would therefore have the same effect, as that originating in the body itself.

A study of the various charts shows that there was no consistent change in either estrogen or androgen excretion after progesterone injection. These materials cannot then be conversion products of progesterone, nor does the second rise in estrogen excretion seem to be due to a release of stored estrogens by progesterone. However, while their production and excretion is not primarily dependent upon the action of progesterone itself, the estrogens which rise so definitely in the presence of its normal production must have their origin in tissues stimulated by the same mechanisms which stimulate the manufacture of the luteal hormone.

In the case of the two sterile women no benefit re-

sulted from treatment with progesterone, although in one case (*M. H.*) the dosage was carried to levels which produced more pregnandiol than in the normal cycle. It would seem therefore that normal progestational stimulation of the uterus was insufficient to bring about implantation.

Since Huber and Davis (41) found similar cases of sterility relieved by gonadotropin of pregnant mare's serum, it would seem that the fault is probably in a failure of ovulation. If ovulation did occur, however, then the metabolism of estrogens indicated by the second rise in the normal cycle, must be necessary for implantation. Further studies are being carried on to determine the effect of the gonadotropic hormone in these cases.

Injection of gonadotropic hormone of pregnant mare's serum. Injections of single doses of 30 Corner units of gonadotropic hormone from pregnant mare's serum showed disturbances in the estrogen excretion in the two subjects so treated. In the subject in which the injection was given immediately after menstruation (*E. Z.*) there was only one large peak during the ensuing period. In the normal subject where the injection was given one week after menstruation there was a prolongation of the first peak with only a short second one. It is interesting to note that this did not appear to influence the appearance of sodium pregnandiol glucuronidate. Table 1 indicates that the early injection of a single dose of gonadotropic hormone increased the output of estrogen in the first maximum although not necessarily the total amount during the period.

While there was evidence of the influence of 30 U of gonadotropic hormone on the estrogen output, this did not show any significant influence on either the androgen or sodium pregnandiol glucuronidate output. Davis and Koff (42) and Siegler and Fein (43) have reported optical evidence of follicular rupture and luteinization after single injections of 30 to 60 U. On the other hand Frank (44) using a similar technic was unable to confirm these findings. The original condition of the ovaries in these individuals was of course not known. Siegler (45) reported changes in the endometrium which he interpreted as due to luteinization brought on by a series of injections of the same gonadotropic hormone totaling 60 to 80 U per cycle. In three instances sodium pregnandiol glucuronidate was determined. It is not clear whether the compound was found after injection in all cases where it was not present before, but the statement is made that the finding of 4 mg. under these conditions was taken as a positive response. Huber and Davis (41), using much larger doses (120–160 U) report endometrial changes indicative of progesterone action together with the relief of sterility in at least three cases. It seems probable that our dosage was sufficient to stimulate follicular development above that normally present without inducing significantly increased luteinization. Experiments are now under way to determine whether larger and more prolonged administration will cause increased excretion of sodium pregnandiol glucuronidate.

SUMMARY

In normal women there is a definite double peaked cycle in the excretion of estrogenic material when measured by injecting mice with a glycol stearate suspension. The first peak is sharper and is probably associated with ovulation.

The second peak appears to be associated with the development of the corpus luteum, since this rise did not occur in two women with poor progesterone formation who had normal first peaks. Sterility was not relieved in one woman when injected with sufficient amounts of progesterone to restore normal pregnandiol excretion. The other showed relief of premenstrual edema after such treatment but the effect on sterility was not determined.

Two women with oligomenorrhea and irregular menses showed normal estrogen excretion and approximately normal pregnandiol output, but abnormally high excretion of androgens. The total output of active substances was twice that of normal women.

The injection of progesterone caused increased excretion of pregnandiol but did not appear to influence the estrogen or androgen curves. It seems, therefore, that the increased estrogens of the second half of the period do not originate from, nor are influenced by, progesterone. Restoration of the complete menstrual cycle requires the injection of estrogens as well as progesterone during the second half of the menstrual cycle.

Injection of 30 Corner units of the gonadotropic hormone of pregnant mare's serum increased the output of estrogenic substances but did not seem to affect progesterone output. The follicle stimulating effect therefore seems to be more easily produced in women than the luteinizing action.

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STILBESTROL

CLINICAL EFFECT OF STILBESTROL ON POSTPARTUM ACTIVITY OF THE MAMMARY GLANDS

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SINCE the introduction of stilbestrol many observations have been reported on the effect of this estrogenic substance on human lactation and breast engorgement. The present study has centered primarily around the effect of stilbestrol on breast engorgement and to a lesser degree with its effect on milk secretion before and after lactation has been established.

MATERIAL

One hundred postpartum women have been treated for breast engorgement. Forty-six were multiparas and 54 primiparas. The age range was from 15 to 48 years with the distribution as listed below.

No. of cases	Age, years
30	15 to 20
33	21 to 25
12	26 to 30
11	31 to 35
12	36 to 40
2	41 to 48

Eighty patients were given 4, 4-hydroxy-alpha-beta-diethyl-stilbene[1] orally as enteric coated tablets, while the remaining number received uncoated tablets. Treatment was continued from 1 to 6 days. In the majority of instances therapy was begun from 12 hours to 2 days postpartum as listed below.

No. of cases	Time postpartum medication begun
33	12 hours postpartum
46	First day postpartum
12	Second day postpartum
8	3 to 4 days postpartum
1	2 months postpartum

The indication for drying up the breasts was elective in 80 cases; severe illness of the mother in 11; inverted nipples in 2; while in the remaining 7 it was given to observe the effect on lactation after milk secretion had been established.

RESULTS

Table 1 notes the reactions observed in 92 patients, 37 of whom were multiparas. It is apparent that the more successful results came with larger doses of stilbestrol. However, the majority of complete or partial failures occurred when therapy was instituted more than 24 hours postpartum, or when the total dosage was small (5 to 10 mg). If treatment was begun within the first 24 hours after delivery and a larger dose was distributed over a longer period there was less breast engorgement and more effective suppression of lactation. This latter observation needs confirmation because some patients normally have little, if any, milk, but still may have considerable breast distention. Among 75 patients receiving no treatment, 2 women had no milk but showed marked engorgement, while 2 others had scant lactation but no mastalgia.

TABLE 1. THE RELATIONSHIP OF THE EFFECT OF STILBESTROL ON BREAST ENGORGEMENT TO THE TIME OF ADMINISTRATION OF STILBESTROL POSTPARTUM AND TO THE DOSAGE OF THE DRUG

No. cases	Postpartum day treatment begun	No. days treated	Total dose, mg.	No engorgement	Mild to moderate engorgement	No effect
41	1st 24 hours	1	5	24	13	4
11	1st 24 hours	1	10	5	4	2
2	2nd 24 hours	1	15	0	2	0
6	1 to 3 days	1 to 2	20	3	2	1
18	1 to 2 days	3	25	12	6	0
9	1 to 2 days	3 to 4	30	6	3	0
2	1 day	4	35	1	1	0
1	2 days	3	40	0	1	0
3	1 day	5 to 6	45 to 50	3	0	0

When lactation had been established, the amount of engorgement was not noticeably altered although by administration of the drug milk secretion was appreciably diminished. This was particularly noted in 7 women not included in the table, in whom persistent distention of the breasts with excessive lactation was associated with pain. These patients were each given 10 mg. of stilbestrol daily to a total of 20 to 40 mg. In 4 the breasts became soft, but continued to lactate, while in the other 3 lactation was inhibited partially so that there was insufficient milk for the infant. After stopping treatment the milk supply returned gradually to normal within 2 to 3 days. In approximately 16% of the group either the initia-

Received for publication April 8, 1941.

[1] Supplied as stilbestrol by E. R. Squibb & Co. through the courtesy of Dr. J. R. Morrell.

tion of lactation or engorgement or both was delayed, sometimes as long as 8 days after medication had been discontinued. This suggests that the inhibitory effect of stilbestrol would be more satisfactory if medication were extended over a period longer than 2 or 3 days, and if the dosage were diminished gradually rather than stopped abruptly.

DISCUSSION

Comparable results in either the prevention or inhibition of lactation or both have been obtained by various observers (1–23) with doses varying from 2 to 100 mg. of stilbestrol given over a period of 1 to 7 days. The reason for the existing confusion is well stated by Abarbanel and Klein (1): "Clearly, then, the process of lactation resolves itself into two fundamental mechanisms—first, the initiation of lactation by hormonal factors, and, second, the maintenance of established lactation by both hormonal and neurogenic agencies."

Various investigators (1–14) generally agree that breast engorgement can be prevented more effectively when administration of stilbestrol is begun within the first 24 hours postpartum. Analysis of available data indicates that 10 mg. a day for 3 to 5 days will insure the most satisfactory result. Once lactation has been established the amount of breast distention can be either diminished or the period of engorgement shortened or both but not eliminated entirely. Leinzinger with 6 to 20 mg. of Cyren B (stilbestrol dipropionate) over the 3- to 4-day period before lactation began noted successful results in approximately 50% while satisfactory effects were obtained in only 33% where drug administration was started after milk secretion was established. Where medication was begun after lactation was established and the baby was permitted to nurse at regular intervals, milk secretion continued normally even though as much as 500 mg. of stilbestrol were given per week. On the other hand, if the drug was administered before the initiation of milk flow and the baby continued to nurse regularly, lactation was delayed 2 to 7 days after the last dose of stilbestrol (1). Our limited observations on 7 cases do not entirely confirm the former point. When the baby was never put to breast, milk secretion appeared 1 to 8 days after medication was discontinued, or as long as 12 days after delivery. This was particularly true in patients with a history of being "heavy milkers." Similar results have been recorded (3, 10, 15). Muckle found that 40% showed some lactation 4 to 5 days after treatment was stopped.

Several toxic effects have been recorded as appearing in from 1 to 80% of the non-peurperal patients receiving stilbestrol. The most frequent side effect has been nausea and vomiting (16–20). Additional subjective and objective reactions include skin rashes, abdominal distress, diarrhea, paresthesias, marked thirst, vertigo, lassitude, psychotic reaction (21), marked swelling of the lower extremities and hematometra and hematocolpos (22).

Among data collected on more than 650 puerperal women receiving stilbestrol only one toxic reaction has been recorded; edema of the vulva (11). In one of our patients who was given 5 mg. of stilbestrol twice in a single day 2 months after delivery, in an attempt to inhibit lactation, nausea and vomiting demanded discontinuance of the drug. This woman was evidently far enough postpartum to react in the manner of a non-puerperal individual. During pregnancy and for several days postpartum stilbestrol is undoubtedly metabolized in a different manner than at other times so that toxic reactions seldom occur.

SUMMARY

One hundred postpartum women were given stilbestrol orally so that the effect on breast engorgement and on lactation might be observed. If the administration of the stilbestrol is begun within the first 24 hours postpartum and continued for 5 days (10 mg. daily), breast engorgement will be prevented in most cases; the initiation of lactation, however, is usually delayed but not inhibited entirely.

No satisfactory explanation is forthcoming as to why toxic reactions occur less frequently among postpartum patients than with non-puerperal individuals.

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I. ANDROGENIC EFFECTS AND THE PRODUCTION OF GYNECOMASTIA AND OLIGOSPERMIA

METHYL TESTOSTERONE

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NINETEEN MEN have been treated with oral methyl testosterone for periods ranging from two weeks to ten months. Of these, 11 have been treated for 4 months or more and 6 for 2 months or less. There were 11 cases of testicular deficiency: 9 of eunuchoidism, 1 of infantilism and 1 of a suprasellar cyst. In addition, there were 7 cases of functional impotence, 1 of which had associated severe Grave's disease. The remaining case was of pseudohermaphrodism.

Androgen assays were normal in all of the 7 cases treated only for impotence. There was no clinical evidence of endocrine disorder in any of these except in the one with hyperthyroidism. In none was the impotence improved by treatment. The dose of methyl testosterone[1] has varied from 25 to 300 mg. per day in 25 mg. tablets.

CASE PROTOCOLS

Case 1 (W.He.).[2] A white man 28 years of age, had sustained an injury to the testicles on two occasions when he was 14 years of age. This was followed by testicular atrophy. The voice had changed somewhat before the testicular atrophy but genital growth and secondary sex characteristics were retarded. Libido was minimal and impotence almost complete.

He measured 70¾ in. in height, had a span of 72 in., and weighed 188 lb. The skin was extremely smooth and fine. Axillary and pubic hair were sparse. There was no beard. The penis measured 10 cm. from the pubic bone to the tip. Testicular tissue was not palpable and the prostate was extremely small.

The basal metabolic rate was −20%. The urinary androgen excretion in two 24-hour periods was 25 and 14 I.U. respectively. A roentgenogram showed a normal sella turcica. Visual fields were normal.

A diagnosis of prepuberal hypogonadism was made.

Treatment with oral methyl testosterone was started in doses of 75 mg. per day, and never exceeded 100 mg. per day. Erections and libido were markedly stimulated within 4 days. At the end of 2 weeks of treatment almost constant erections necessitated temporary withdrawal of the drug for a few days. The prostate and penis were distinctly larger in 3 weeks. The treatment was withdrawn for 18 days and the number of erections gradually subsided to the original level. The commencement of therapy again produced an effect similar to that previously noted.

After one month of treatment there was an increase in beard growth. Over a 6-month period during which treatment was given for about 4 months, the penis increased 5 cm. in length and the prostate grew to more than one-half normal size as determined by rectal palpation. There was some increase in body hair.

The B.M.R. rose from a low level of −23% to a level of +2%, at which time he was taking 100 mg. of methyl testosterone daily. The weight increased from 188 lb. to 206 lb. The greatest weight was recorded at the time the B.M.R. was +2%. The urinary androgens did not increase while he was taking 75 mg. per day, as assays on two 24-hour specimens showed 13 and 16 I.U. respectively.

Case 2 (S.I.).[3] A white man, 30 years of age, was first seen in 1936 at which time he had a severe eunuchoidism of congenital origin. He failed to respond to 6400 U of pregnancy urine extract given over a period of a little over two months in 1937.

Subsequently he showed striking improvement from the use of testosterone propionate injections, which were given from April, 1937, until June, 1939 in doses varying from 10 mg. to 50 mg. 3 times a week.

Approximately one year after cessation of testosterone propionate therapy he returned to the Clinic. There had been complete loss of potence and libido during this period. Examination showed his height to be 68¾ in., his span 71½ in., and his weight, 146 lb. His general body habitus approached that of a normal male except that there was excessive girdle fat, a sparse beard, and female distribution of pubic hair. The penis was smaller than average, measuring 7 cm. from the pubic bone to the tip. The left testis measured 1.5 by 5 cm. and the right gland was not palpable. The prostate which had approximated normal size at the end of therapy with testosterone propionate was now minute. The voice was deep and masculine.

Received for publication February 24, 1941.

[1] Methyl testosterone, as Oreton-M, and testosterone propionate, as Oreton, were supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. E. Schwenk and Dr. M. Gilbert.

[2] This case is discussed further in the second paper of this series on calorigenic activity.

[3] This case is discussed further in Papers II and III of this series.

Androgen assay levels of 2 and 9 I.U. were found initially and during treatment with testosterone propionate were distinctly within normal limits. A single dose of 47 mg. of methyl testosterone failed to reduce any increase in urinary androgens when measured on the 1st, 2nd, 3rd, 5th and 7th days after administration.

At the time he was first seen the B.M.R. was −21%. While he was receiving 25 mg. of testosterone propionate by injection 3 times a week, it was found to be −3% on one occasion. Prior to treatment with methyl testosterone the B.M.R. was measured on 3 occasions and found to be −20, −21, and −28%. Two hundred milligrams of methyl testosterone was given daily. The B.M.R. progressively rose to +4% in 1½ months. The pulse rate increased little if any and there was a weight gain of 25 lb.

Libido and potence were restored to normal levels after 4 days of treatment. The first erection in 10 months occurred on the morning of the fifth day of treatment. Breast tissue was first palpated after 30 days of treatment. At the end of 6 weeks the penis had grown 1 cm. and the prostate had increased distinctly in size.

Studies of sodium chloride, and nitrogen excretion before and during treatment were made in this case, and are to be reported in detail in a later paper. The data we have available in this case at present seem to indicate that there is a definite retention of nitrogen and chloride during the administration of methyl testosterone.

Case 3 (*B.H.*).[4] A white man, 22 years of age, had noted a cessation of sexual development at the age of 14. Trauma to the left testicle had occurred at that time. Secondary sexual characteristics had failed to appear. He experienced only occasional erections and had never had an ejaculation. Body growth continued at the rate of three-fourths of an inch during the preceding year. There were no signs suggestive of pituitary disease, hypothalamic injury or hypothyroidism. He was 67¾ in. tall with a span of 71 5/8 in. He weighed 118 lb. His demeanor was retiring. The facies were puerile. There was no beard or visible hair on the trunk or extremities. Pubic and axillary hair approximated one-third normal. The penis measured 7.3 cm. from the pubic bone to the tip. The right testis measured 2 cm. by 1.5 cm. and the left testis 2.0 cm. by 1.0 cm. The prostate was barely palpable.

A roentgenogram of the skull revealed no enlargement of the sella turcica, and the visual fields were normal. The epiphyseal age was 17 years. There was a measurable amount of gonadotropic hormone by urinary assay. The B.M.R. was −29%. Numerous capon assays for urinary androgens revealed consistently low levels. A diagnosis of eunuchoidism was made.

Some improvement occurred with the continued use of gonadotropic hormone between October, 1939 and April, 1940. Methyl testosterone orally was then started in doses varying between 75 and 150 mg. daily. Symptomatically there was definite improvement. Erections increased within a week from about twice weekly to twice daily. At the end of 6 weeks the voice was changing and the penis had increased from 7.3 cm. to 8 cm. in length. In 3 months muscular development was greater and there was a slight increase of hair on the limbs. The testes were unchanged. The B.M.R. rose from −29% to −2% in 15 days when he was taking 150 mg. of methyl testosterone daily. The urinary androgens fell from a level of 38 I.U. while he was receiving gonadotropic hormone to 11 I.U. while he had been taking 75 mg. of methyl testosterone daily for 16 days and 100 mg. daily for 13 days. The symptoms were better controlled at the time of the low assay. The body weight increased 8 lb. within a period of several weeks.

Case 4 (*T.K.*).[5] A white man, 19 years of age, complained of failure to mature properly. He had experienced no heterosexual inclinations, and erections or nocturnal emissions had never occurred. He was 71½ in. tall with a span of 75 in., and he weighed 149 lb. The facial appearance was boyish. The voice pitch was preadolescent. His demeanor was unassuming. A very few pubic and axillary hairs were present, and there was virtually no hair on the trunk and extremities. The penis measured 5.5 cm. from the pubic bone to the tip. Testes could not be felt and the prostate was not identified with certainty. The B.M.R. was −10%. The assay result for urinary androgens was 11 I.U. The epiphyseal age was 15 years. The sella turcica was normal.

A diagnosis of prepuberal hypogonadism was made.

Methyl testosterone, 75 mg. daily, was given for 34 days. The dose then was increased to 150 mg. daily for 10 days and for the past 4 months he has received 200 mg. per day. Symptomatically there was striking improvement within a week. Erections occurred at least daily. Within 2 months the voice was lower in pitch, and at the end of 5½ months, it had continued to change but was not normal. The penis grew 2 cm. in 2 months and at the end of 5½ months had grown 3.5 cm. The prostate was palpable after 2 months of treatment and was approximately one-half the normal size by 5½ months. Mild acne was present in 2 months and has persisted. He has grown 1¼ in. in height in 5½ months and has increased 24 lb. in body weight. Gynecomastia developed after 2 months of treatment and has persisted but not increased. In 3 months there was no apparent change in epiphyseal maturity. Axillary and pubic hair have increased. Assays for urinary androgens while on treatment have been 15 and 17 I.U. at which times his symptoms were well controlled. The B.M.R. has risen from −10% to +22%.

Case 5 (*T.S.*). A white man, 21 years of age, was first seen in July, 1937 at which time he complained of failure of testicular growth following a testicular injury at the age of 12 years. Potence was at a low level and nocturnal emissions never had occurred. The voice had changed to some extent, but was not masculine. His height was 68½ in., span 71½ in., and weight 134 lb. The skin was very fine. There was no beard, very sparse body hair, no axillary hair, and pubic hair of female distribution. The penis measured 8.5 cm. and the testes 1.5 cm. by 1.5 cm. each. The prostate was minute.

The B.M.R. was −13%. A roentgenogram of the sella turcica showed it to be normal, and visual fields were normal. Assay result for urinary androgens was 16 I.U. A diagnosis of definite but mild eunuchoidism was made.

Treatment with a total of 30,000 U. of gonadotropic

[4] This case is discussed further in Paper II of this series.

[5] This case is discussed further in Paper II of this series.

hormone from September to December, 1937 produced no change.

Testosterone propionate was administered in doses varying between 10 and 50 mg. 3 times a week for 2 years. During this time potence was normal and definite anatomical changes occurred. The facies appeared more mature but there was little beard growth. The voice was normal. Body hair was sparse. Axillary hair had appeared and had increased to a normal amount. Pubic hair had increased. The penis appeared normal, measuring 10 cm. The prostate had grown to one-half to two-thirds of normal size. The testes had not changed in size. An ejaculate appeared.

Methyl testosterone therapy was carried on over a period of 4 months on doses of 25 mg. to 100 mg. per day. Symptoms were well controlled. Little or no anatomical changes were observed as his physical status so nearly approximated the normal. The assays for urinary androgens are of some interest. During treatment with testosterone propionate by injection, the urinary androgens were distinctly in the normal range. However, when methyl testosterone was administered symptoms were also well controlled and the assays were distinctly low.

Case 6 (J.D.).[6] A white man, 27 years of age, was a typical eunuchoid who had no evidence of any endocrine abnormality which could not be explained on the basis of his hypogonadism.

He had received large doses of testosterone propionate by injection over a period of 2 years and had improved remarkably. His physical status approached that of a normal male except that he had very little beard and a small prostate. During testosterone propionate therapy the penis grew from 3 cm. to 8.5 cm. Both testes descended and apparently enlarged. The prostate which had not been palpable grew to one-third normal size. The previously sparse axillary and pubic hair became normal in amount and the beard which was absent approximated one-half the normal amount. Methyl testosterone has been given intermittently for 11 months in dosages varying between 300 and 500 mg. per day. Potence and libido have been maintained at a normal level and energy and endurance have improved. Gynecomastia developed at the end of 5½ months of treatment, and has persisted. The prostate has increased slightly in size. Beard growth is fairly definite.

Body weight has decreased 8 to 10 lb. The B.M.R. which was −16% at the start of treatment rose as high as +38%. At this time there were none of the usual signs of hyperthyroidism and the pulse rate was only 74 beats per minute. The rise and fall in the basal metabolic rate has been consistent with the administration and discontinuance of the drug. Assays for urinary androgens have been as low as 11 I.U. when he was receiving as much as 300 mg. of methyl testosterone per day, and at which time symptoms were well controlled.

Case 7 (H.D.).[7] A white man, 39 years of age, developed bilateral testicular atrophy following orchitis associated with epidemic parotitis at the age of 13 years. There was no evidence of any endocrine disease which could not be explained on the basis of his eunuchoidism. Considerable improvement had resulted from treatment with large doses of testosterone by injection given for over two years. He received no treatment for 5½ months prior to the beginning of methyl testosterone therapy. Potence at that time was at a low level. His physical status approached the normal except that he had little beard and a small prostate.

Methyl testosterone has been given intermittently during the past 9 months in doses varying between 25 and 150 mg. per day. Energy and endurance increased within a week after starting therapy, as did the number of erections and amount of ejaculate. There has been a slight increase in the size of the prostate and penis. The beard definitely has increased.

Body weight increased 9 lb. The B.M.R. was found to be −27% on 3 occasions before testosterone propionate was given, and was found to be −17% when he was receiving 50 mg. 3 times per week. Prior to the start of methyl testosterone therapy, the B.M.R. was −29%. An assay for urinary androgen was performed when the symptoms were well controlled and was found to be 8 I.U.

Case 8 (F.W.).[8] A white man, 29 years of age, had developed bilateral testicular atrophy following an operation for cryptorchidism at the age of 15 years. He had no evidence of any endocrine disease which could not be explained on the basis of his eunuchoidism. He was given large doses of testosterone propionate by injection for over two years and had improved remarkably. He had not received any treatment for 4 months prior to the beginning of treatment with methyl testosterone, and had noted a decrease in energy. Erections occurred about once a month. He did not appear as mature as his chronological age. The skin was very fine. Body, axillary and pubic hair were sparse. There was no beard. The penis measured 7.5 cm. from the pubic bone to the tip. No testicular tissue was palpable and the prostate was about one-third normal size. The voice had changed somewhat but was not masculine in type.

An assay for urinary androgen at this time showed 24 I.U. The B.M.R. was −21%. Methyl testosterone has been given intermittently during the past 12 months in doses varying between 75 and 300 mg. daily. Assays for urinary androgens have been made on 5 occasions and have shown levels varying between 5 and 31 I.U. while receiving treatment. The B.M.R. has increased to +3% during treatment. Body weight has increased 22 lb.

Two days after the beginning of treatment, erections were occurring daily and general body energy and endurance were increased. The penis increased 3.5 cm. in length during the first month and has been stationary in size since then. The prostate increased to one-half to two-thirds normal size in 4 months. Gynecomastia was first noted after 4 months of therapy and has persisted. The beard, body, axillary and pubic hair have increased and acne has appeared. There appears to be a definite increase in the size of the muscles.

Case 9 (T.M.).[9] A white man, 33 years of age, ap-

[6] This case is discussed further in Paper II of this series.
[7] This case is discussed further in Paper II of this series.
[8] This case is discussed further in Papers II and III of this series.
[9] This case is discussed further in Paper II of this series.

peared to be in his late teens. His appearance was that of a typical eunuchoid. He stated that he never had had an erection nor nocturnal emissions, and that he had grown some in the last 5 years. He shaved once a week. He had a past history of pulmonary tuberculosis and cervical tuberculous adenitis which was quiescent. Symptoms referable to his hypogonadism antedated the tuberculous infection. The larynx was small and the voice pitch high. He had a very slight beard, and the pubic hair was moderate and of female distribution. The skin was very fine. The prostate was just palpable and the penis measured 5.2 cm. The left testis was extremely small and the right testis was not palpable.

He was given testosterone propionate by injection in doses varying from 10 to 25 mg. 3 times a week for 22 months, during which time he improved remarkably. The penis grew from 5.2 cm. to 9 cm. The left testicle was unchanged and the right one descended to the lower end of the inguinal canal. The prostate grew moderately. Voice change was only slight. He had normal erections.

Methyl testosterone orally in doses of 100 mg. per day was begun in April, 1940, After 4 months of such treatment he had a mild gynecomastia. The prostate has grown considerably. There have been no penile changes. Symptoms have been well controlled.

A bioassay for urinary androgens before treatment revealed 2 I.U.; during the treatment with 25 mg. of testosterone propionate by injections three times a week, 36 I.U. and during oral administration of 100 mg. of methyl testosterone daily, 13 I.U.

Case 10 (*W.Ho.*).[10] A white man, 24 years of age, complained of progressive visual loss for 10 years. Hypogonadism was readily discernible, as evidenced by the very fine skin, no beard, sparse body hair, genitalia smaller than the average normal, and a small prostate. Visual fields showed a complete loss of vision in the left eye and a temporal loss in the right eye. Fundoscopic examination revealed bilateral primary optic atrophy which was greater in the left eye. A roentgenogram of the sella turcica revealed a depressed, irregular floor with erosion and elevation of the posterior clinoids. Tolerance to glucose as determined by a single oral dose of 100 gm. was slightly increased. The B.M.R. was −28% and −30% on two occasions. Assay for urinary androgens was 13 I.U.

A right frontal craniectomy was performed and a supracellar cyst evacuated. Microscopic section of the cyst wall showed it to be a craniopharyngioma. Ten weeks postoperatively the B.M.R. was −27%. Assay result for urinary androgens was 17 I.U. He then was started on 75 mg. of methyl testosterone daily. There was marked improvement in the low level of potence. Methyl testosterone therapy was discontinued after one month because of marked increase of headache. The B.M.R. rose to −12% in 3 weeks and urinary androgens were unchanged being 14 I.U.

With the discontinuance of androgen therapy, the headache promptly subsided. It seems reasonable to speculate that this may have been due to increased intracranial pressure associated with retention of electrolytes and water. The weight increased 18 lb. in 4 weeks.

Case 11 (*E.B.*).[11] This patient was a white man, 19 years of age, who had failed to grow properly and in whom there was unmistakable evidence of hypogonadism. This case is reported in detail to show the effect of methyl testosterone on growth in the third paper of this series.

Case 12 (*S.K.H.*). A white man, 44 years of age, complained of depression and undue fatigue with a low level of libido and potence for 5 years. Upon physical examinations there were no significant findings.

The basal metabolic rate was normal. The assay result for urinary androgens in a 24-hour specimen was 28 I.U.

A diagnosis of functional impotence was made.

Testosterone propionate by injection in doses of 25 mg. three times a week followed by methyl testosterone orally in doses of 75 to 125 mg. per day failed to produce any improvement.

Case 13 (*E.L.C.*). A white man, 30 years of age, complained of gradual loss of potence. A polyp had been removed from the verumontanum without improvement. There was no evidence of chronic prostatitis. His general health was excellent. The genital development and secondary sex characteristics were normal. The basal metabolic rate and urinary androgen level were normal.

A diagnosis of functional impotence was made.

He was treated with various gonadotropic hormone preparations without improvement. Methyl testosterone was administered in a dosage varying from 75 to 200 mg. per day. There was no increase in potence.

The weight increased 11 lb in several months and the B.M.R. increased to +27% during treatment. Curiously enough he developed a mild gynecomastia one week after cessation of therapy. Aspermia was produced while he was taking 200 mg. of testosterone propionate daily.

Case 14 (*S.G.*). A white man 51 years of age, complained of complete loss of potence for about 5 years. Libido was normal. General examination revealed nothing of significance other than a blood pressure of 178 systolic and 120 diastolic. Secondary sex characteristics were normal as was the external genitalia and prostate. The androgen assay determination on a 24-hour urine sample was 28 I.U.

A diagnosis of functional impotence was made.

He had received some testosterone propionate therapy before coming to us, but had had no improvement. He was given a 4 weeks' trial on methyl testosterone in doses of 75 mg. daily for 2 weeks and 100 mg. daily for 2 weeks. His body weight increased 4½ lb. during this time. There was no symptomatic improvement.

Case 15 (*H.J.*). A white man, 56 years of age, who had severe hypertension with coronary artery disease, complained of loss of libido and impotence. Physical examination revealed no evidence of hypogonadism. The androgen assay levels were low; namely, 0.0 and 14.0, but he was quite ill from his vascular disease at this time.

Treatment with testosterone propionate by injection resulted in normal urinary androgen levels, but no improvement in potence or libido.

[10] This case is discussed further in Paper II of this series.

[11] This case is discussed further in Paper II of this series.

He recently suffered a coronary occlusion. During his hospital stay, he was given methyl testosterone orally in order that its effect upon the basal metabolic rate and blood count might be noted. The B.M.R. rose from −18% to +1% in 20 days on doses varying from 50 to 250 mg. per day. Symptomatically there was no improvement.

Case 16 (*A.D.*). A white man, 37 years of age, complained of almost complete impotence with normal libido of several years' duration. His general health had been excellent. On physical examination there were no significant findings other than a mild chronic prostatitis.

The basal metabolic rate was normal. The urinary androgen excretion was found to be as high as 55 I.U. in 24 hours.

A diagnosis of functional impotence was made.

The prostatitis was adequately treated with slight if any improvement of symptoms. Large doses of gonadotropic hormone were given for two months without improvement.

Methyl testosterone was administered in doses varying from 75 to 200 mg. daily. The weight increased 5 lb. There was no improvement in potence.

Case 17 (*A.F.*). A white man, 44 years of age, noted increasing impotence over a 4-year period of time. There had been no change in libido. Secondary sexual characteristics were normal. The external genitalia and prostate also were normal. The remainder of the physical examination as well as laboratory studies revealed nothing of significance. The B.M.R. was −4%. The assay result for urinary androgens was 26 I.U. A modified Friedman test showed measurable gonadotropic substances.

A diagnosis of functional impotence was made.

Therapy consisted of 2.5 mg. of testosterone propionate 3 times a week for 3 weeks in the latter part of 1936, and 10 mg. 3 times a week for 3 weeks in the latter part of 1937, without improvement.

Methyl testosterone was given in doses varying from 75 to 150 mg. daily for 2 weeks in April, 1940. There was no improvement. An increase of 4 lb. in body weight in this time was noted.

Case 18 (*H.H.*). A white man, 56 years of age, had had typical Grave's disease with symptoms for 4 months. There was an associated loss of libido and potence.

The B.M.R. was +50%. Assay for urinary androgens showed 26 I.U. A total of 1350 mg. of methyl testosterone and 1250 mg. of testosterone propionate by injection was administered over a period of 17 days. The B.M.R. varied between +41% and +68%. There was no improvement of libido and potence or symptoms associated with the hyperthyroidism. During this period he was placed upon a fixed caloric intake. The accountable weight gain was less than one pound; however, he did gain a total of 10 lb. in the 17 days.

Case 19 (*T.F.*). A white man, 23 years of age, complained of nocturnal enuresis, a low level of potence, and gynecomastia. On examination he was found to be mentally retarded. He was 65 in. tall with a span of 67½ in., and weighed 127½ lb. The genitalia were smaller than average normal. The penis measured 6 cm. and hypospadias was present. On either side of the median raphe of the scrotum there were two projections of tissue 1½ in. by 1 in. which appeared much like labia minora. The prostate was minute. The breasts measured 5 cm. in diameter. The beard was sparse, axillary hair was normal, and pubic hair was female in distribution. A complete investigation of the urinary tract revealed no abnormalities.

Estrin assay showed 20 to 30 R.U. per daily output of urine. The Friedman test result was negative. An oligospermia was present. Repeated urinary assays for androgen revealed levels consistently ranging between 50 and 63 I.U.. He was given a total of 30,000 U. of pregnancy urine extract over a period of 5 months, without improvement. Methyl testosterone was given over a period of 9 months in doses varying from 75 to 150 mg. daily. There has been no change in the size of the breasts nor other anatomical changes of note except slight growth of the prostate. There has been a questionable increase in potence, and the nocturnal enuresis continues.

Androgenic Effects

Striking androgenic effects have been present in the 11 cases which showed evidence of testicular deficiency. Foss (1) has reported similar observations. The effects are closely comparable to those seen following the injection of testosterone propionate. Methyl testosterone given orally in doses of 75 mg. daily produces a symptomatic response very similar to that produced by injection of 25 mg. of testosterone propionate 3 times a week. The maximum symptomatic response can be obtained from a dose of approximately 150 mg. per day.

The penile erections markedly increase in number

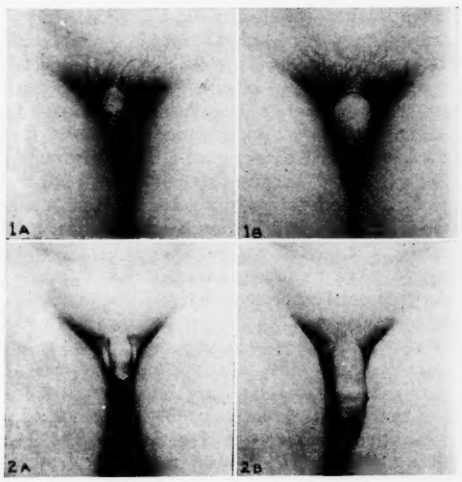

Fig. 1. PENILE GROWTH RESULTING FROM 3 MO. TREATMENT WITH METHYL TESTOSTERONE (*Case 4, T. K.*). A. 3/15/40. METHYL TESTOSTERONE 4/6,—75 MG. PENIS 7.5 CM. IN LENGTH, 8.2 CM. IN CIRCUMFERENCE. B. 6/7/40. METHYL TESTOSTERONE 5/10,—150 MG. PENIS 8.0 CM. IN LENGTH, 9.5 CM. IN CIRCUMFERENCE.

Fig. 2. PENILE GROWTH RESULTING FROM 6½ MO. TREATMENT WITH METHYL TESTOSTERONE (*Case 11, E. B.*). A. 2/5/40. METHYL TESTOSTERONE 2/7,—50 MG.; 5/22,—200 MG. PENIS 4 CM. IN LENGTH. B. 8, 26/40. METHYL TESTOSTERONE 3/6,—100 MG.; 10/31, —300 MG. PENIS 8.5 CM. IN LENGTH, 8.5 CM. IN CIRCUMFERENCE.

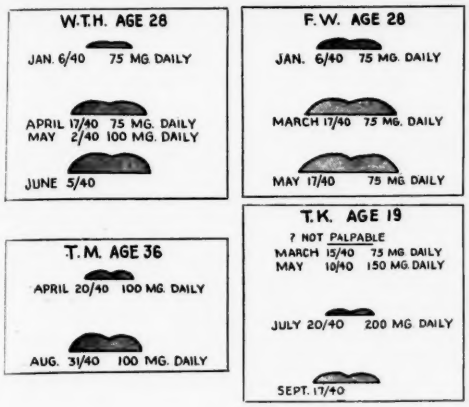
W.T.H. AGE 28
JAN. 6/40 75 MG. DAILY
APRIL 17/40 75 MG. DAILY
MAY 2/40 100 MG. DAILY
JUNE 5/40
F.W. AGE 28
JAN. 6/40 75 MG. DAILY
MARCH 17/40 75 MG. DAILY
MAY 17/40 75 MG. DAILY
T.M. AGE 36
APRIL 20/40 100 MG. DAILY
AUG. 31/40 100 MG. DAILY
T.K. AGE 19
? NOT PALPABLE
MARCH 15/40 75 MG. DAILY
MAY 10/40 150 MG. DAILY
JULY 20/40 200 MG. DAILY
SEPT. 17/40

Fig. 3. PROSTATIC GROWTH IN EUNUCHOIDS TREATED WITH METHYL TESTOSTERONE.

and power on the third or fourth day of administration of the hormone. In some cases excessive erections necessitate temporary withdrawal of therapy. The response in sexual potence diminishes to approximately normal within about two weeks upon continuation of the same dosage.

Within a week of the initiation of treatment, the sense of well being and energy distinctly increase and continue throughout treatment. The previous retiring and shy demeanor changes to one which is aggressive and normally masculine.

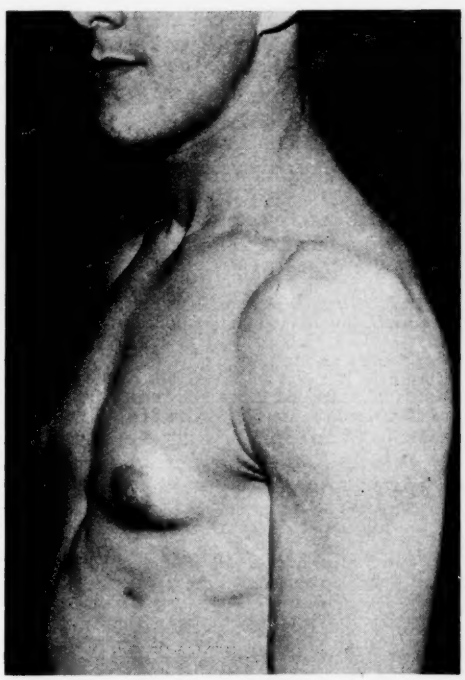

Fig. 4. GYNECOMASTIA RESULTING FROM TESTOSTERONE THERAPY.

Penile growth and the growth of the pubic and axillary hair are obvious in the course of a few weeks (fig. 1, 2). There is a gradual increase in the amount of hair on the limbs and trunk.

The prostate grows distinctly and in most cases responds well to doses of 75 mg. per day. Examples of prostatic growth, as judged by rectal palpation, are shown in figure 3. These diagrams are taken from sketches in our records of the approximate size of the prostate as recorded at the time of the interval examinations. They were made by the same examiners. Although these diagrammatic representations are not morphologically exact there was no doubt in the authors' minds that the prostatic growth was as great as these visual representations indicate. In one case (*W.He.*) the prostate grew from approximately one-fourth normal size to relatively normal size in 6 months on 75 to 100 mg. of methyl testosterone per day. In case *T.M.* the prostatic growth shown in the chart is greater than it had been previously on injections of 25 mg. of testosterone propionate 3 times a week, and in *F.W.*, greater than it had been on the injection of 50 mg. of testosterone propionate 3 times a week. An ejaculate may appear for the first time within a few days after beginning therapy, and nocturnal emissions appear in some of the cases for the first time.

The typically puerile facies gradually take on an appearance of maturity. Facial acne may appear as early as the first or second week of treatment with doses of 75 mg. per day. It tends to increase paralleling the size of the dose and usually will disappear in approximately 2 weeks after cessation of treatment. We have seen it persist much longer in some patients who have taken larger doses. The increase in beard growth is slow. There is apparently little or no response to doses less than 150 mg. per day, and in no patient has a distinct increase in beard growth been noted in less than approximately 4 months. The larynx grows and the voice becomes rough and deeper pitched. In one patient this was distinct in 1 month of treatment and in another, within 2 months.

There is an easily discernible increase in the size of the skeletal muscles, especially about the shoulder girdle. Weight gain has occurred in every case except one in which there was a marked increase in the basal metabolic rate. The average weight gain in 14 cases in which accurate records were kept was 14 lb., the minimum being 3 lb. and the maximum, 31 lb. In some cases the growth rate is increased strikingly and a rate of growth as high as 3.7 in. per year was seen over a period of 8 months. The problems of weight gain and growth are discussed in more detail in the third paper of this series.

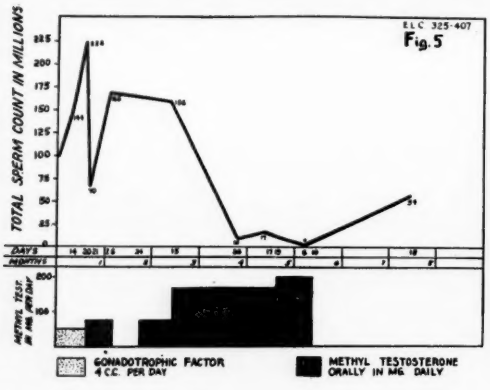

Fig. 5. Effect of methyl testosterone on sperm count in a case of functional impotence (*Case 13*).

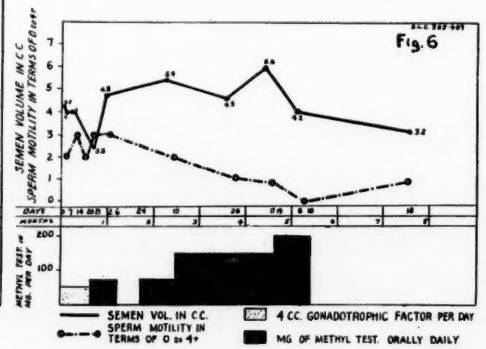
Fig. 6
SEMEN VOLUME IN C.C.
SPERM MOTILITY IN TERMS OF 0 to 4+
DAYS
MONTHS
METHYL TEST IN MG. PER DAY
SEMEN VOL. IN C.C.
SPERM MOTILITY IN TERMS OF 0 to 4+
4 C.C. GONADOTROPHIC FACTOR PER DAY
MG. OF METHYL TEST. ORALLY DAILY

Fig. 6. Effect of methyl testosterone on semen volume and sperm motility in a case of functional impotence (*Case 13*).

An inconsistent anatomical change following the use of methyl testosterone is the appearance of gynecomastia. It appeared in 6 of the 11 patients with hypogonadism. In the patient in whom it appeared earliest (*S.I.*) the condition was first noted in thirty days. He had received 200 mg. per day. In one (*F.W.*) it was not noted until 75 mg. per day had been taken for 16 weeks.

Among the 5 patients who did not develop gynecomastia, one had received an average dose of 132 mg. per day for 17 weeks. It occurred in the one case of pituitary infantilism. Gynecomastia also developed in one patient with impotence who had no symptoms of hypogonadism.

The breast tissue, when first noted, consisted of slightly nodular, tender, rounded masses beneath the areolae. Continuation of treatment led to masses as large as 3 cm. in diameter and 1.5 to 2 cm. in thickness. In one case the breast tissue extended outward toward the axilla (fig. 4). No secretion has been noted. Similar gynecomastia has been noted by Selye et al. (2) in normal and castrated male rats following the injection of testosterone benzoate.

Methyl testosterone apparently has the power to produce oligospermia similar to that shown to occur following the intramuscular use of testosterone propionate (3, 4, 5). An illustrative case is shown (fig. 5, 6). Figure 5 shows the fall in sperm production and in figure 6 it will be noted that sperm motility parallels the count. The semen volume is little affected. All of the semen specimens examined were collected following periods of 5 or more days of continence, and were examined within one hour of collection. The specimens were collected in a glass container and were kept at room temperature.

SUMMARY

Peroral methyl testosterone produces in male hypogonadism the appearance of secondary sexual characteristics, including increased potence, growth of the penis and prostate, and an increase in body and facial hair. An ejaculate appears. The pitch of the voice becomes lower. The demeanor becomes masculine and there appears to be an increase in the size of the skeletal muscles. Facial acne appears. Energy and endurance are increased. Gynecomastia is produced in some cases. Oligospermia has been observed following treatment.

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II. CALORIGENIC ACTIVITY

METHYL TESTOSTERONE

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CERTAIN EFFECTS not ordinarily considered androgenic have become increasingly apparent in the course of observations on the use of methyl testosterone[1] in cases of male hypogonadism. One of the most striking of these is its effect upon the basal metabolic rate.

The calorigenic effect of androgens has been mentioned previously in the literature but has not been emphasized. Kenyon et al. (1) found an elevation of the basal metabolic rate in 7 of 8 eunuchoids treated with testosterone propionate and considered the elevation, although slight, "too consistent to be disregarded." A rise of 6 to 14 points in the basal metabolic rate was found in their cases.

Subsequently, Kenyon (2) found more marked increases in the basal metabolic rate occurring over a period of months and amounting to as much as 38% increase in eunuchoids treated with testosterone propionate. Thompson and Heckel (3) reported an increase in the basal metabolic rate above normal range following the administration of testosterone propionate in a case of eunuchoidism.

Kochakian (4), and Kochakian and Murlin (5, 6) found an elevated basal metabolic rate in only one of a series of dogs treated with urinary androgens. Galli (7) found no significant increase in normal human subjects treated with testosterone propionate over a period of 6 days.

Ten cases in which the calorigenic activity[2] of methyl testosterone was observed are discussed. Some other activities of the drug are mentioned.

Case 2 (S.I.).[3] A young man, 34 years of age, previously had been treated successfully for eunuchoidism with testosterone propionate. He had received no treatment for 11 months. During that time he had noted a marked diminution in energy and endurance, a loss of sexual potence, and the prostate, which under previous treatment had attained normal size, again had become atrophic.

On July 16, 1940 he entered the Hospital. After certain metabolic studies were made he was given 200 mg. of methyl testosterone orally daily beginning on July 28. In four days erections, which had been absent for many months, appeared and subsequently were frequent. He noted an increased sense of alertness and energy. The changes in B.M.R., pulse rate, and body weight are presented in figure 1. The pulse rates given are averages of

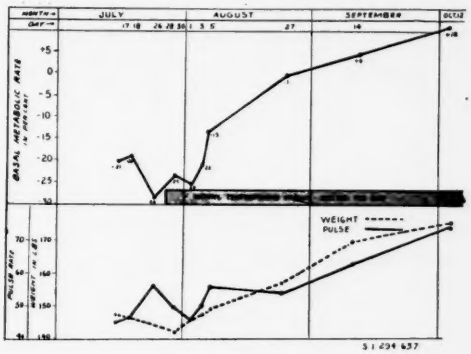

Fig. 1. CALORIGENIC ACTION OF METHYL TESTOSTERONE. (*Case 2. S.I.*)

those taken during each basal metabolism test. There was an apparent accumulative effect of the drug upon the basal metabolic rate for at least 6 weeks. The attendant rise in pulse rate is relatively slight. There was no definite change in blood pressure during this period, the representative blood pressures being: July 15, 105/50; July 18, 107/70; August 3, 110/70; September 14, 100/65. The sense of well being persisted. There was no gastrointestinal distress, no evident edema, and no suggestive signs of drug toxicity. By August 8, mild gynecomastia had appeared.

Case 6 (J.D.)[4] is an example of severe prepuberal hypogonadism. He is 31 years of age. He previously had a dramatic response to testosterone propionate therapy, which was discontinued in August, 1939. Two hundred mg. of testosterone was implanted subcutaneously on August 19, and again on August 31.

The use of testosterone propionate was resumed in doses of 50 mg. 3 times weekly between October 16, and January 2, with a prompt return of clinical improvement. Testosterone propionate therapy was discontinued on January 2, 1940. On January 29, peroral methyl testo-

Received for publication, February 24, 1941.

[1] The methyl testosterone, as Oreton-M, and testosterone propionate as Oreton, were supplied by the Schering Corporation, Bloomfield, N. J., through the courtesy of Dr. E. Schwenk and Dr. M. Gilbert.

[2] Each basal metabolism test represents two runs; the Sanborn graphic machine was used and calculations were based on the Aub-Dubois tables.

[3] This case is discussed further in Papers I and III of this series.

[4] This case is discussed further in Paper I of this series.

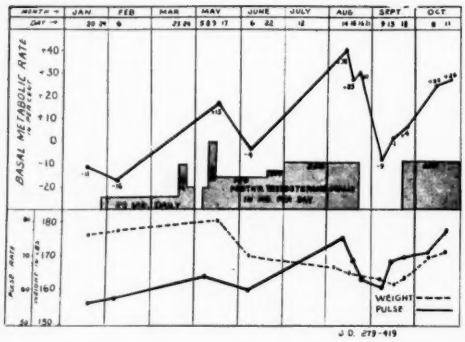

Fig. 2. CALORIGENIC ACTION OF METHYL TESTOSTERONE. (*Case 6. J.D.*)

sterone therapy was begun in the doses indicated in figure 2.

The clinical response to methyl testosterone was striking. Within 2 weeks erections became frequent, and increase in energy was obvious, nocturnal emissions appeared and the amount of ejaculate gradually increased. The external genitalia grew larger and the prostate increased slowly in size. During July, gynecomastia appeared.

On August 15, his basal metabolism was found to be high, and he appeared more restless than usual. The facies were rather anxious and a mild flush was present. The conjunctivae appeared slightly injected. The presence of digital tremor was so slight as to be questionable. The skin was moist but this seemed of little significance since the weather was hot. The pulse rate was 72 when taken in the office and the blood pressure was 105 systolic, 70 diastolic. The hypermetabolism was not accompanied by the clinical picture expected from thyroid feeding or thyroid stimulation sufficient to cause such a rise in the basal metabolic rate.

This is the only case in which the metabolic rise has been associated with weight loss. It suggests that fat oxidation associated with the increased metabolic rate was more than sufficient to overcome weight gain produced by retention of water, electrolytes and nitrogen. His weight on January 29 was 188 lb; April 1, 191; May 16, 187; June 22, 179; August, 168; August 15, 166. Treatment was discontinued on August 21 and by September 13 gynecomastia, erections, and increased sense of energy had disappeared. The B.M.R. on September 9 was −9%; on September 13, +1%; and on September 18, +4%. On September 18, he began to take 250 mg. of methyl testosterone per day and on September 25, the dose was increased to 300 mg. per day. The basal metabolism on October 8 had risen to +22% and on October 11, to +26%.

TABLE 1. *Case 7 (H.D.)* HYPOGONADISM

Date	Androgen dosage	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1932 Dec.		−24	160	
1933 Feb.		−28		
1935 Dec.		−27	192	
1938 Jan.		−27	196	
Testosterone Propionate Intramuscularly				
May 13	25			
July 20	50			
Sept. 20	25			
Oct. 3		−18		
Oct. 30	50			
Dec. 6		−17	198	57
1939 Feb. 8	50 (3×wk.)			
Therapy stopped Oct. 10, 1939				
1940 Feb. 23		−29	194	57
Methyl Testosterone Orally				
1940 Feb. 24	50			
Mar. 27	100			
Apr. 3		−15	197	69
Aug. 7		− 6	207	56
Aug. 8	150			
Sept. 24		− 8	203	68

In this and in the following tables, a date given with no statement as to methyl testosterone dosage means continuation of the previous amount.

TABLE 2. *Case 8 (F.W.)*[1] HYPOGONADISM

Date	Androgen dosage	B.M.R.	Weight	Pulse
	mg.	%	lb.	
1937 July 24	20	−21	115	68
July 25				
Oct. 16	20	−14	117	72
1938 Feb. 14	35			
May 7		−11	128	67
July 9	25			
1939 Jan. 21	25			
Therapy stopped Aug. 14, 1939				
Dec. 1		−14		
1940 Jan. 6		−21	125	71
Methyl Testosterone Orally (daily)				
1940 Jan. 7	75			
Feb. 12	50			
Mar. 1	75			
Mar. 19	100			
Apr. 9	75			
Apr. 13		− 8	147	76
Aug. 31	125	− 9	145	75
Sept. 20		− 6		
Sept. 21	200			
Oct. 12		+ 3	147	78

[1] This case is discussed further in Papers I and III of this series.

TABLE 3. *Case 4 (T.K.)*[1] HYPOGONADISM

Date	Methyl testosterone, orally	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1940 Apr. 6		−10	149	73
Apr. 7	75			
May 10	150			
June 8		+13	165	80
June 9	200			
July 20			173	74
Sept. 17		+22	173	84

[1] This case is discussed further in Paper I of this series.

TABLE 4. *Case* 10 (*W.Ho.*)[1] HYPOGONADISM. SUPRACELLAR CYST

Date	Methyl testosterone	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1939 Nov. 28		−30	188	58
Nov. 29		−28	188	66
Dec. 6	(Evacuation of supracellar cyst)			
1940 Feb. 27		−27	199	64
Mar. 5	75			
Mar. 20	75	−12	209	67
Apr. 19		−19	219	55

[1] This case is discussed further in Paper I of this series.

Case 7 (*H.D.*)[5] was a case of eunuchism which followed orchitis associated with epidemic parotitis at the age of 13 years. At present he is 39 years of age. After receiving testosterone propionate during 1938 and 1939, his genital maturity and secondary sexual characteristics closely approximated normal. From the figures shown in table 1, it seems that testosterone propionate in the doses indicated raised the B.M.R. approximately 10%, and that it fell to its previous levels following cessation of therapy. At

TABLE 5. *Case* 9 (*T.M.*)[1] HYPOGONADISM

Date	Methyl testosterone	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1937 Nov. 24		−14	100	82
1939 Nov.			117	
1940 Apr. 21	100		120	
to Sept. 14		−2	120	68

[1] This case is discussed further in Paper I of this series.

TABLE 6. *Case* 3 (*B.H.*)[1] HYPOGONADISM

Date	Methyl testosterone	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1939 Sept.		−29		
1940 Apr. 2			115	
Apr. 11	75			
May 3	100			
May 16	125	− 3	120	73
Therapy discontinued June 1, 1940				
1940 June 13		−13	121	68
1940 June 18	150			
July 2		− 4	123	66
Therapy discontinued July 11, 1940				
1940 July 25		−29	121	66
1940 Aug. 1	150			
Aug. 16		− 2	123	72
Oct. 19		− 3	126	64
Oct. 28	300			
Nov. 16		− 3	129	70

[1] This case is discussed further in Paper I of this series.

[5] This case is discussed further in Paper I of this series.

TABLE 7. *Case* 1 (*W.He.*)[1] HYPOGONADISM

Date	Methyl testosterone	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1939 Nov. 1		−20	191	54
1940 Jan. 6	75			
Jan. 24	50			
Jan. 30		−12	204	64
Jan. 31		−10	203	64
Feb. 1		−12	202	60
Therapy discontinued Feb. 1, 1940				
1940 Feb. 20		−23	199	56
1940 Apr. 17	75		190	
May 2	100			
June 3		− 4	230	58
June 11		+ 2	206	63

[1] This case is discussed further in Paper I of this series.

no time did he show any clinical evidence of thyroid deficiency. Desiccated thyroid was given in doses of 1 grain per day from January to August, 1938, but at no other time in the course of treatment indicated in the chart.

The distinct rise in the basal metabolic rate, together with an increase in weight and little change in the pulse rate while the patient received methyl testosterone is indicated. There never was a significant alteration in the blood pressure.

The remaining cases are instances of rather marked prepuberal hypogonadism. Two of these had evidence of pituitary disease; one had a suprasellar cyst; and the other was a case of infantilism. The accompanying tables indicate clearly the same type of effect upon the basal metabolism, pulse rate, and body weight as that commented upon in the preceding cases.

DISCUSSION

A striking effect of methyl testosterone in the doses used is its ability to raise the basal metabolic rate. The

TABLE 8. *Case* 11 (*E.B.*)[1] INFANTILISM

Date	Methyl testosterone	B.M.R.	Weight	Pulse
	mg./day	%	lb.	
1939 Apr. 14	(Thyroid, desiccated, 1 grain/day)	− 9	65	68
1940 Feb. 5	50			
Mar. 6	100			
May 22	200			
June 1		− 9	78	60
Aug. 26		+ 5	80	65
Therapy discontinued Aug. 27, 1940				
1940 Sept. 20		−11	76	62
1940 Sept. 25	200			
Oct. 14	300			
Nov. 1		− 8	79	67

[1] This case is discussed further in Papers I and III of this series.

data shown in *cases* 3 and 4 show a similar calorigenic action to be a property of testosterone propionate. Whether or not the effect is comparable if equal doses of the two preparations are given parenterally or orally remains to be shown.

Such increases in the basal metabolic rate usually are associated with a gain in weight. Studies to be reported indicate that some of this is due to water, chloride and nitrogen retention. The nitrogen retention is pronounced and strongly suggests the deposition of new tissue favoring growth.

The rise in the basal metabolic rate was a consistent finding in all of the cases studied. The minimum rise was 12% and the maximum, 54%. The average maximum rise in the 10 cases reported was 27.6%. A minimum rise was calculated, using as extremes the highest pretreatment level and the lowest level obtained after the dose had reached its height. The average of such figures is 18.6%. A very small response was present in the case of infantilism (*case* 10). This was true on two occasions following large doses for more than 5 weeks.

The rate of response is suggested by some of the cases. In *case* 1 there was a distinct rise in 8 days of treatment and in *case* 8, in 2 weeks. This rise may continue for several months while the same dose is being given. A fall in B.M.R. from −4 to −29% occurred in 2 weeks in *case* 8 following withdrawal of therapy. In *case* 9 the rate fell from −12 to −23% in 19 days.

The extent of the rise is roughly 10% following the use of 75 mg. per day, and 20 to 25% following the use of 150 mg. per day, in periods of 3 weeks or more.

A weight gain accompanied the metabolic rise in every patient but one (*case* 2). In this patient the basal metabolic rate was the highest and the weight loss probably was a result. In general the extent of weight gain has not been correlated with the degree of metabolic increase. Very little rise in pulse rate has been observed. In some of the patients (*cases* 1 and 2) a distinct increase in the pulse rate accompanied an elevation of basal metabolism of over 30%; however, in *case* 9 there was an increase of 26% in the basal metabolic rate with no increase in the pulse rate.

In no instance has any significant change in blood pressure been noted. Even when the basal metabolic rate is as high as +38% the clinical picture does not resemble hyperthyroidism.

Although methyl testosterone cannot be recommended as a calorigenic agent for general clinical use at this time, the probable clinical importance of such a property is obvious and invites further investigation.

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METHYL TESTOSTERONE

III. EFFECT UPON BODY WEIGHT AND GROWTH

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THE ADMINISTRATION of various steroids is known to be associated with a gain in body weight. For example, this has been shown to be an outstanding characteristic of desoxycorticosterone (1). In a case under our observation, the injection of 20 mg. per day caused weight gain as high as 14 lb. in 3 days. Such weight gain has been shown to be associated with retention of sodium, chloride, and water. Other steroids have similar properties, although their effect in this respect is less marked.

Kenyon (2) noted a gain in body weight following the use of testosterone propionate and showed this to be associated with retention of sodium, chloride, water, and nitrogen. These findings were corroborated by McCullagh and McGurl (3). The administration of testosterone propionate has caused weight gain in some of our cases.

Gain in weight has been a consistent finding in our cases treated with methyl testosterone.[1] These changes in body weight are referred to in the second paper of this series. The weight gain has not continued during the entire treatment period in these cases, but has increased rapidly in the first six or eight weeks following which there is a tendency to "plateau" (fig. 1, 2).

It has been recognized clearly for some time that the administration of androgens causes growth of the genitalia and, in this sense, they are growth hormones. It also has been known that the presence of the testes in the body is associated with certain changes in the muscular system. In eunuchoidism the muscles are underdeveloped and their contours are soft compared with those of a normal man. In some of our cases of eunuchoidism which have been treated with testosterone propionate for several years, there has been a gradual and unmistakable change in the appearance of the muscle contours. Before treatment the arms were slender, the chest narrow, and the neck relatively thin and rounded. After many months of treatment, the pectoral muscles become more prominent, the deltoid muscles more prominent, and the sternocleidomastoid muscles definitely stand out against the overlying skin. In this sense also androgens may be considered growth hormones.

The administration of androgens to eunuchoids also produces definite growth of body, facial, axillary and pubic hair. In individuals treated with large doses of testosterone propionate and methyl testosterone, the skin changes from an atrophic, parchment-like appearance to a thicker, more hyperemic, more velvety, oilier, and more moist skin, indicating stimulation of the cells and glands of the skin.

At puberty there is both a rapid increase in rate of growth and in the rate of steroid production closely

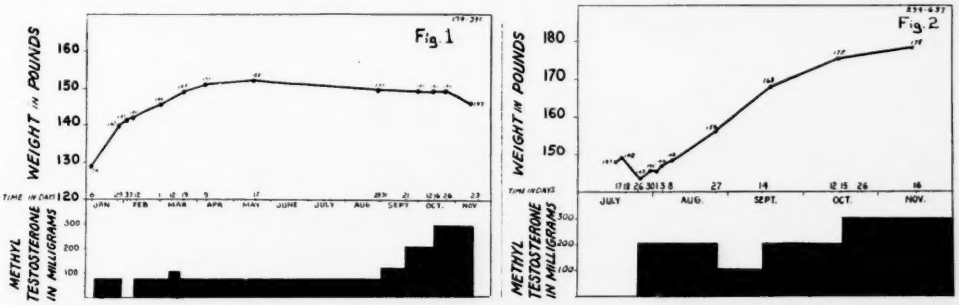

Fig. 1, 2. WEIGHT GAIN DURING METHYL TESTOSTERONE THERAPY. Fig. 1. *Case 8. F.W.* Fig. 2. *Case 2. S.I.*

Received for publication February 24, 1941.

[1] Methyl testosterone, as Oreton-M, and testosterone propionate, as Oreton, were supplied by the Schering Corporation, Bloomfield. N. J., through the courtesy of Dr. E. Schwenk and Dr. M. Gilbert.

related to those under discussion. It is significant also that in certain cases of adrenocortical tumor, the rate of growth is increased to a point considerably in excess of normal. In such instances which have come to our attention there has been a very striking increase in the amount of urinary androgens as well as estrogens. This suggests that steroids of adrenocortical origin possibly are responsible for the stimulation of growth.

In consideration of linear bodily growth there are usually thought to be two chief growth hormones: the growth factor of the pituitary and the thyroid hormone. Under certain circumstances, androgens have a powerful growth stimulating effect. In several of our patients, there has been evident stimulation of growth accompanying the administration of testosterone propionate and methyl testosterone. Webster (4) reported 8 cases in which there was an increase in the rate of growth following the use of testosterone propionate. He did not demonstrate any increase in the rate of epiphyseal closure. These two changes may occur concomittantly, however, in cases of adrenal tumor with juvenile andrenogenital syndrome, and also if large doses of testosterone propionate are used (3).

The case described below illustrates the growth effect of methyl testosterone.

CASE PROTOCOL

Case 11.[2] The patient (*E.B.*) is a white male. He was born April 9, 1921 and weighed 8 pounds, according to the mother's statement. At 7 months of age he was noted to be small, and has been small for his age since that time. Tonsillectomy and adenoidectomy were performed at the age of 3 years. He had measles at 6, mumps at 7, and whooping cough at 8 years of age. There were no other diseases of any consequence.

Between the ages of 8 and 10 years, he had three or four "spells" a year which began with a headache, accompanied by what was thought to be a fever. He would grind his teeth, perhaps vomit, and finally become unconscious (sleep?) for two or three hours. There never were any generalized convulsions.

He had three sisters younger than himself. All were normal in size, as were both parents.

When first examined at the age of 12 years and 8 months, his height was 47 in. and weight 48½ lb. His temperature was 98.6° F., the pulse rate was 80, and the blood pressure was 85 systolic and 55 diastolic. His stature was small but proportions were good. The facial structures were not proportionately as small as those sometimes seen in dwarfism. The skin was clear and pale. The teeth were relatively small and crowded, and the dental age was calculated to approximate the normal at the age of 8 or 9 years. There was no goiter. The chest, heart and abdomen were normal. The penis was smaller than average for his age. He had noted no erections. There were no signs of puberty. The right testis was not descended fully, but could be palpated high in the inguinal canal.

The fundi oculi, visual fields, and roentgen examination of the sella turcica showed no abnormalities. A Friedman test made on concentrated morning urine produced hemorrhagic follicles (2+) in the test rabbit. Urinalysis and Wassermann and Kahn test results were negative. The blood sugar was 128 two hours p.c. Blood counts showed 4,530,000 red cells with 84% hemoglobin, and 7,900 white cells. A basal metabolism test on December 8, 1933 was calculated by the Aub-Dubois standards to be −19%.

A diagnosis of dwarfism was made. Because of the smallness of the genitalia and the cryptorchidism, this was thought to be of pituitary origin.

Treatment and Subsequent Course

Thyroid medication. Desiccated thyroid was begun in December, 1933 and was continued in dosages varying from ¾ gr. per day to 1½ gr. per day until after January, 1938. The exact date of its discontinuance is not clear from the record. The basal metabolic rate never has been distinctly below normal since that time but has been at its highest level while the patient was receiving methyl testosterone without desiccated thyroid. The approximate rate of growth while the patient was taking desiccated thyroid and no other therapy is shown in table 1.

Previous to beginning the use of methyl testosterone, other forms of therapy were tried, including polyvalent anterior pituitary extract.[3]

TABLE 1. THYROID DOSAGE AND THE BASAL METABOLIC RATE

Date	Therapy	B.M.R.
		%
	Desiccated Thyroid	
12/ 8/33	1 gr.	−19
12/29/33	1 gr.	− 5
3/29/34	1 gr.	−10
8/27/36	1 gr. ss.	−16
10/ 4/36	1 gr. ss.	± 0
2/ 9/37	¾ gr.	−21
2/20/37	1 gr. ss.	
? ? ?		−28
7/16/37	1 gr. ss.	− 8
1/21/38	1 gr.	− 8
4/14/39		− 9
	Methyl Testosterone	
2/ 5/40	50 mg./day.	
3/ 6/40	100 mg./day.	
4/22/40 to 5/10/40	100 mg. (Oral testosterone propionate)	
5/22/40	200 mg./day	
6/ 1/40	200 mg./day	− 9
8/25/40	200 mg./day	+ 5
9/20/40	200 mg./day	−11
11/ 1/40	200 mg./day	− 8
11/27/40	200 mg./day	− 4

[2] This case is discussed further in Papers I and II of this series.

[3] Anterior pituitary extract, as Polyansin, and pregnancy urine extract, as A.P.L. were supplied by Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

TABLE 2. BIOASSAYS FOR ANDROGEN
(Method by McCullagh and McLin)

Date	Androgens	Therapy
	I.U.	
1937— 8/4	0	Desiccated thyroid 1 gr. ss. q.d.
1939— 4/6	2	PU extract, 500 U 3×wk.
4/21		Discontinued.
9/21		
9/23	2	
9/30	2	
10/24		PMS 1 cc.
11/5	3	
11/20	8	
11/29	8	
12/10	11	
12/28	4	
1940— 1/21	0	
2/1		Discontinued.
2/5		Methyl testosterone 50 mg. daily.
2/23	7	
3/6		Methyl testosterone 100 mg. 4×daily.
3/21	11	
4/22		Discontinued.
5/4	9	
5/10		Methyl testosterone 100 mg. 4×daily.

TABLE 3. EFFECT OF METHYL TESTOSTERONE UPON MATURITY AND LINEAR GROWTH

Date	Methyl testosterone, orally	Maturity changes	Height
	mg./day		*in.*
1940— 2/7	50	Penis length 4 cm. Prostate not palpable.	53.2
3/6	100	Penis length 7 cm. Prostate palpable Pubic hair slight.	
4/21	Discontinued.		
4/22 to 5/10	(Oral testosterone propionate given)		
5/10	100		54.1
5/22	200	Voice lower	54.2
6/26		Pubic hair increased. Gynecomastia.	
8/1	200	Penis length 7.5 cm.	
8/26		Penis length 8.5 cm. Breasts larger.	55.7
11/28	300	Prostate ¾ normal. Erections frequent. Nocturnal emissions.	56.3

Pituitary extract. Injections of anterior pituitary extract were begun in October, 1937. At that time there were no signs of maturity. The right testicle was not palpable and the left testicle was in the upper scrotum. The penis measured 4.0 cm. from the pubis to the end of the prepuce. One-half of 1 cc. (50 U) of anterior pituitary extract was given daily until April, 1939. In October, 1937 his height was 51 in.; in April 1938 it was 51 7/8 in., an increase of about 1¾ in. per year. No other changes were noted.

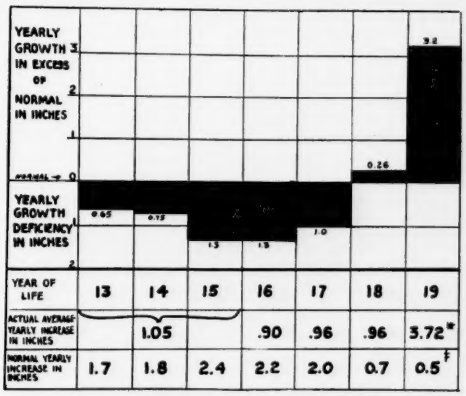

Fig. 3. INCREASE IN GROWTH RATE IN A HYPOGONADAL DWARF TREATED ORALLY WITH METHYL TESTOSTERONE. Normal is the medium height of short boys from the weight-height-age tables of Baldwin and Wood (Iowa Child Welfare Research Station, Iowa City).* The growth during the 19th year was calculated from a 10-month period during which he took methyl testosterone.† Normal measure in height for the 19th year is an estimation calculated from normals of preceding years.

Pregnancy urine extract. In April, 1939 injections of pregnancy urine extract[3] were begun, and were continued at the rate of 500 U 3 times weekly from April 21, 1939 until September 18, 1939. In April his height was 52¼ in., the penis was 5.5 cm. in length, the right testis was not palpable, and no signs of puberty were noted. In September his height was 52¾ in.; he was unchanged otherwise.

Pregnant mare's serum extract. Pregnant mare's serum extract[4] was given approximately three times weekly in doses of 1 cc. between October 24, 1939 and February 1, 1940. In February, 1940 his height was 53½ in. There was no increace in the size of the genitalia nor any signs of maturity.

Up to this time, his average yearly growth approximated one inch per year, but reached levels as high as one and a half to one and three-fourth inches a year during periods of therapy with pituitary extract and gonadotropins.

Bioassays for urinary androgens were made from time to time but always were found to be at very low levels and failed to rise after androgen in physiological doses was administered in the form of oral methyl testosterone (table 2).

[3] See footnote on page 508.

[4] Pregnant mare's serum extract, as Gonadin, was supplied by the Cutter Laboratories, Berkeley, California.

Methyl testosterone. The oral administration of methyl testosterone was begun on February 5, 1940. A synopsis of the doses and the maturity changes up to November 28, 1940 are included in table 3.

It is to be seen from table 3 that following the administration of methyl testosterone, this patient not only showed signs of sexual maturity but also his rate of linear growth increased to between three and four times its previous rate. The actual increase in rate of growth following the use of methyl testosterone can be seen in figure 3.

From estimates of epiphyseal age made on roentgenograms taken in 1936, 1937, 1939, and three times in 1940, it appears that the epiphyseal maturity has been advancing more rapidly during 1940 than previously, and there is suggestive evidence that it is more rapid than the normal rate.

SUMMARY

Illustrations have been presented showing the increase in weight which has accompanied the use of methyl testosterone in two other cases of testicular deficiency.

Attention has been called to the several growth effects of androgens.

A case of dwarfism has been presented. Between the ages of 12 and 19 years, he grew approximately one inch per year. During this time he had received desiccated thyroid to tolerance over several years, and various other forms of treatment had been tried. During nine and a half months of almost continuous therapy with oral methyl testosterone he has increased in height at the rate of 3.9 inches per year.

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GYNECOMASTIA

THE HYPERTROPHY OF THE MALE BREAST

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GYNECOMASTIA, hypertrophy of the male breast, has been extensively described in the literature of the last century. However, its etiology has been shrouded in mystery and all the hypotheses concerning it have been of a purely speculative nature. It was only with the progress in endocrinology that a rational basis was established for investigation of this condition.

Studies of the sex hormones have revealed that the male and female sex hormones are closely related and that both are present in either sex. The influence of the sex hormones on the normal and pathological development of different organs, particularly of the breast, has been established. The mutual relationship between the sex glands and those controlling metabolism and growth has been noted. It was this knowledge of hormonal activity that stimulated experimental studies of gynecomastia which have brought us closer to a real understanding of its etiology.

The vast number of cases which have been published hitherto describe gynecomastia as accompanying some apparently unrelated condition such as obesity, diseases of the testes, brain tumors, lung tumors and tuberculosis. Few of the specimens have been examined histologically and almost none of the cases were subjected to thorough hormonal studies. The purpose of this paper therefore is to define clearly the concept of gynecomastia and to correlate some of the clinical observations with the known endocrinological data.

TRUE GYNECOMASTIA

True gynecomastia represents a localized, often painful swelling of glandular consistency, adherent to the nipple. Usual size is approximately 2 to 3 cm. in diameter, but occasionally it reaches larger proportions.

According to Menville (1), who examined the material of the Johns Hopkins Clinic, gynecomastia is unilateral in 87% of the cases. This is attributed to irritation in one breast or trauma, the history of which can be elicited in about 15% of the cases. Assuming an endocrinological etiology for gynecomastia, no satisfactory explanation has been offered yet for its unilateral appearance, though unilateral symptoms are well known in several endocrine conditions.

The most common type of gynecomastia appears in puberty. It seldom achieves conspicuous proportions and usually regresses within a short time. Gruber in 1856 (2) observed the coincidence of gynecomastia with congenital or acquired defects in genitalia, particularly in the testes. Cases of gynecomastia associated with hermaphrodism or other congenital defects in the testes have been published repeatedly. Even more frequent are cases of acquired defects: injuries, tumors, varicocele, atrophies, orchitis following mumps, tuberculosis, gonorrhea. The old theory of Moskowitz (3) was that the testicular secretion inhibits the growth of the male breast. However, the relation is certainly not of such a simple nature. A bilateral orchidectomy does not produce gynecomastia either clinically or experimentally. On the other hand, there is extensive evidence of relationship of gynecomastia to the anterior pituitary and to the adrenal cortex. The interdependence of these endocrine glands is well known. Several cases of pituitary tumors and hyperplasia or tumors of the suprarenal (adreno-genital syndrome) are on record. In most of these cases some pathology of the testes are mentioned. A case was described by Edwards, Shinkin and Shaver (4), in which massive doses of cortex hormone administered in the treatment of Addison's disease caused gynecomastia which subsided when the treatment was discontinued.

Heidrich (5) found 8 cases of gynecomastia among the 140 cases of teratoma testes. Ferguson (6) had 5 gynecomastia cases in his series of 117 teratomas. In all of Ferguson's cases which were autopsied and in which intravitam pathologic amounts of gonadotropin were found, basophilic hyperplasia of the pituitary could be demonstrated. This hypoplasia is similar or identical with the pituitary adenoma in pregnancy. Hyperemia and swelling of the adrenals were also regularly noted. According to Ferguson, those teratoma patients who seemed to be cured or free from disease for a period of years, establish a

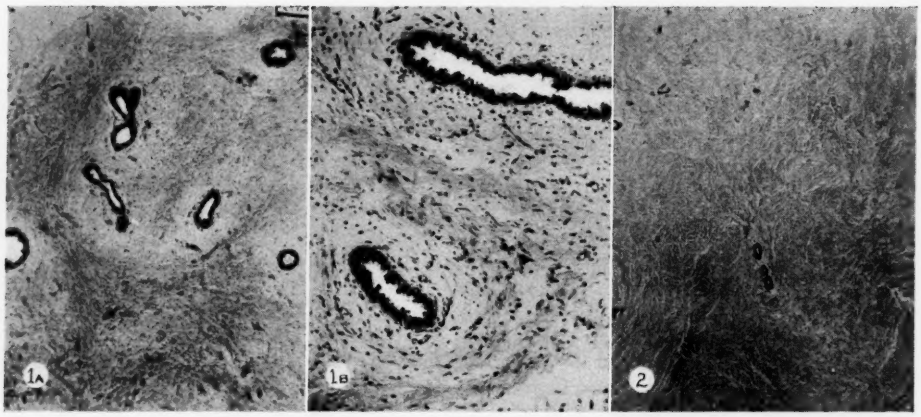

Fig. 1A. Low power photomicrograph (23 ×) of breast tissue in male from a case of true gynecomastia, showing the proliferation of the ducts and periductal connective tissue. Note the resemblance to pericanalicular fibroadenoma.
Fig. 1B. A higher power magnification (65 ×) of an area from the section in fig. 1A.
Fig. 2. Low power photomicrograph (23 ×) of normal appearing breast tissue in male from a case of pseudo-gynecomastia. Compare with figure 1A. (Pathological report by Dr. Arthur M. Ginzler.)

certain level of gonadotropin output. This may be explained by the fact that some of the changes in the pituitary and adrenals persist after the tumor is eradicated. Three cases of unilateral gynecomastia, which developed 1½ years following orchidectomy and x-ray radiation for testicular teratoma were mentioned briefly by Woodham (7). A similar case in our experience warrants a more detailed description.

CASE REPORT

A 28-year-old male patient presented himself in July, 1939 with a swelling of his right breast. The patient had become aware of it two weeks previously. The examination revealed that the swelling was due to a tumor, about the size of a walnut, somewhat sensitive, firm, and sharply localized. It was located underneath and attached to the nipple but freely movable against the underlying structures. There were no palpable glands in the axilla and the other breast was normal. The first impression was that of a gynecomastia. However, the patient gave the history of being operated on his right testis a year and half ago. An inquiry from his urologist revealed that a right orchidectomy was performed because of teratoma and that following the operation the patient received extensive x-ray radiation. The pathological report at that time read: teratoma testis, mixed type with cartilage, fibrous elements and varied epithelial elements. Some parts of the tumor were undifferentiated. The Aschheim-Zondek and Friedman test results were positive before the operation and became negative shortly thereafter.

The patient was thoroughly examined; several x-rays of the skull, chest and long bones were taken and findings were all negative. The other testis appeared to be slightly atrophic and there was a small varicocele, which was present two years ago. The Friedman test result was reported positive with the explanation that the diagnosis was made on the basis of one large hemorrhagic follicle. A few days later the test was repeated and result reported negative.

Because of the obvious possibility of metastasis from teratoma, it was considered essential to verify the diagnosis by exploration and microscopic examination of the tumor.

Through a partial periareolar incision extended toward the axilla, the tumor was dissected and removed, together with the subcutaneous tissue in the axilla. The tumor was found to be attached to the nipple and of benign appearance. There were no lymph nodes in the axilla. The histological diagnosis was: fibroadenoma pericanalicular (fig. 1A, B). The patient made an uneventful recovery and has been well since. The Friedman test result has been consistently negative since the operation. The result of an examination of urine for female sex hormone shortly after the operation was positive in dilution of 1:50, which is rather high, but within normal limits. The sterility test revealed a complete aspermia, which did not respond to any hormonal therapy. This was undoubtedly due to the fact that, despite screening, the remaining testis had received some x-ray radiation after the first operation.

The histology of our specimen (fig. 1A, B) shows that the enlargement of the mammary glands is due solely to the hyperplasia of the ducts and the periductal connective tissue, a picture almost analogous to the fibro-adenoma of the female breast.

McDonald (8) and others demonstrated experimentally on castrated female rats that the injections of estrogen cause the growth and ramification of the ductal apparatus. In order to obtain a proliferation of both elements, acini and ducts, combined injections of estrogen and progesterone are necessary.

Geschickter, Lewis, and Hartman (9) produced gynecomastia experimentally in monkeys by injec-

tion of anterior pituitary extract, but the first reaction was an enlargement of the testes to 2½ times their normal size. The histological examination of such testes showed hyperplasia of the interstitial cells. The anterior pituitary extract was ineffective in castrated animals. The same effect on the breast was achieved by injections of estrogens, but in this experiment no swelling of the testes appeared and the experiment was successful in castrated animals. Small doses of estrogen (15–60 R.U.) given throughout a longer period are more effective than larger doses given during a shorter time. Geschickter's and his co-workers' conclusions are that gynecomastia is due to prolonged hyperstimulation by small amounts of estrogen. The latter or a similar hormone can be produced in the interstitial cells of the testes under the influence of increased activity of the anterior pituitary or in the adrenal cortex. Similarly the etiology of the fibroadenoma of the female breasts lies in hyperstimulation of estrogen.

The interstitial cells in the testis are the source of hormonal secretion. Their hyperplasia is frequently found in atrophic testes and after a mild x-ray irradiation. It is interesting to note that Ferguson found the hyperplasia of the interstitial cells of the unaffected testis in all his autopsied cases of teratoma.

Hunt and Budd (10) described a case of gynecomastia accompanying an interstitial cell tumor. There was a positive Aschheim-Zondek reaction in this case.

Over 70 cases have been reported in the literature of gynecomastia with cirrhosis of the liver. Edmondson and his co-workers (11) mention atrophy of the testes in all of their cases and an increased estrogen excretion in most of them. The authors point out that one of the functions of the liver is the destruction of estrogen. This would explain the increased estrogen level in these cases, but it does not explain why gynecomastia occurs so infrequently in conjunction with cirrhosis.

Applying these studies to the interpretation of our case, we believe to be justified in accepting Geschickter's concept of the development of gynecomastia. The atrophy of the remaining testis and the aspermia predicates a hyperplasia of the interstitial apparatus. The quantitative test of estrogen excretion suggests an abundance of the female sex hormone. The Aschheim-Zondek test results (Friedman's modification) were positive on a few occasions.

Quantitative tests of estrogen and androgen excretion were made by Glass and Bergman (12) on a few cases of gynecomastia. Not all of them showed an increased estrogen output, but the ratio of estrogen to androgen was always substantially altered. Whereas, the average A:E (androgen:estrogen) ratio was 15.3 for males and 2.3 for females, the A:E in gynecomastia was consistently around 5.0.

The treatment of gynecomastia obviously must be directed to the underlying pathology. A thorough general examination and hormone studies are essential, particularly if the primary condition is not apparent. Cases have been known in which the appearance of gynecomastia lead to the detection of a testicular tumor. Certain forms of gynecomastia, i.e. in puberty may be influenced favorably by hormone therapy as was shown by Hoffman and Wernicke with the administration of testosterone. Menville recommends x-ray radiation. However, in a number of cases surgical exploration will be indicated to verify the diagnosis and to exclude the possibility of a metastatic growth. The fear of malignant degeneration of gynecomastia is not justified. Cases of this kind are on record, but they occur in extremely rare instances.

PSEUDOGYNECOMASTIA

Pseudogynecomastia is usually due to some endocrine disorder associated with obesity or a pathological distribution of fat resembling the female pattern. The enlargement of the breasts, characteristic of the obesity of the eunuch is entirely the result of localized fat deposits and not of a hyperplasia of the mammary gland. Pseudogynecomastia as a rule appears bilaterally. It represents a diffuse painless, fairly soft swelling of the breasts which may achieve considerable proportions.

If the basic pathology can be successfully treated with hormonal substitution therapy, the enlargement of the breasts may be somewhat improved, but will never regress completely. For the most part, the patients with enlargement of the male breasts, who seek surgical correction belong to this group. The indication for surgery is the patient's psychological reaction, which is usually one of deep embarrassment and of anxiety because of the implication of loss of virility. The surgical procedure consists in excision of the excessive tissue. If the hypertrophy is very extensive, a simple amputation of the breast is indicated. The preservation of the nipple in the male is by far not as essential as in the female breast. However, in the majority of cases, the nipple can be preserved and need not be grossly displaced. A lateral axillo-pectoral or a sub-mammary incision will allow for an adequate subcutaneous excision of the excessive fat tissue. The microscopic examination of the specimens shows a diffuse hyperplasia of the fat tissue and little, if any, glandular elements of a normal character (fig. 2).

SUMMARY

True gynecomastia and pseudogynecomastia represent independent clinical entities.

In the light of experimental and clinical studies, we are cognizant of the fact that true gynecomastia

is a symptom in several diverse conditions, but we suggest that it is always due to an increased estrogen production (or a decreased androgen:estrogen ratio). The underlying pathology is most frequently in the anterior pituitary or adrenal cortex and in the interstitial cells of the testes.

Pseudogynecomastia may frequently require operative intervention for cosmetic reasons; while the role of surgery in true gynecomastia is limited largely to diagnostic purposes.

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HYPERGENITALISM

HYPERGENITALISM IN A MONGOLIAN IDIOT

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EXCESSIVE GENITAL DEVELOPMENT in a mongolian idiot is a rare occurrence and is especially interesting in view of recent studies (1) indicating that mongolism may be etiologically related to a deficiency of the basophils of the anterior pituitary gland.

Church (2) was of the opinion that because mongols exhibited such strikingly similar symptoms, the underlying factor resided either in the sex or other glands of internal secretion. Timme (3) in 1930 expressed the view that the pituitary played an important role in mongolism. In a female mongol of six weeks Gordon (4) observed histologically the absence of basophils and the prominence of eosinophilic cells.

Since Downs (5) first described mongolism in 1866 (when he found that his patients died of tuberculosis at an early age, rarely living to puberty) there has been little agreement as to the pathogenesis and pathology of mongolism.

Siegert (6) pointed out that many theories (e.g. syphilis) advanced for explaining mongolism have never been proven or have been entirely discarded. Nevertheless the following factors which have been considered, are worthy of mention: an advanced maternal age emphasized by Bleyer (7); the exceedingly high number of mongols that are last-born in large families, Shuttleworth's so-called exhaustion factor; injury or abnormalities in the germ cells or in the fertilized egg (8); and an aging process beginning at the time of liberation of the gamete from the gonads and terminating at the time of fertilization (9).

The brains of mongols studied have been found below normal in size and weight, in addition to presenting diffuse cortical changes and a deficiency in the number and development of convolutions (10). Lind (11) mentions the defects in the brain as part of the picture of mongolism and as not being responsible for other bodily changes.

Benda suggests that mongolism is the result of morphokinetic failure of endocrine origin rather than a monstrosity due to germinal deterioration. In his postmortem studies he found a decrease in the size of the thyroid with involutional changes. Since he felt that the thyroid changes were of pituitary origin, he studied this structure in 14 necropsies. He came to the conclusion, as already suggested, that mongolism was characterized by changes in the anterior pituitary, particularly, insufficiency of the basophilic cells with relative increase in eosinophils and that this was responsible for changes in the other endocrine glands. This is interesting in view of recent work in mongols suggesting the presence of a sufficient amount of growth factor of the anterior lobe of the pituitary (12). Measurements in mongols show growth to be slow but at a low normal level during the first 9 years. Increase in height apparently ceases early and after 14 to 15 years of age few exhibit further advance. In Lind's autopsies some showed atrophy of the thyroid. The state of the pituitary is not mentioned.

Siegert (6) emphasized that defective development of the genitals at birth and in later childhood was one of the most striking features of mongolism reported by most authors. Benda's data on the sexual development of 120 mongolian idiots confirms this finding.

Brousseau (13) remarked that the genitals of both female and male mongols are infantile in development and often remain in a rudimentary state. In males the penis and scrotum are very small, and testes undersized and atrophic, and great delay is experienced in their descent. A statement is made that occasionally the genitals are abnormally large; however, Brousseau was unable to obtain data concerning the functioning

Received for publication December 26, 1940.

of the male sex organs. Benda (14) emphasizes that whereas some male mongols may have strong sexual tendencies and perversions, their chances of being potent are minimal, and it has not been demonstrated that they are capable of fertilization. Autopsies of 3 males 16, 21 and 30 years of age respectively, revealed hypoplastic and degenerated testes and no spermatozoa.

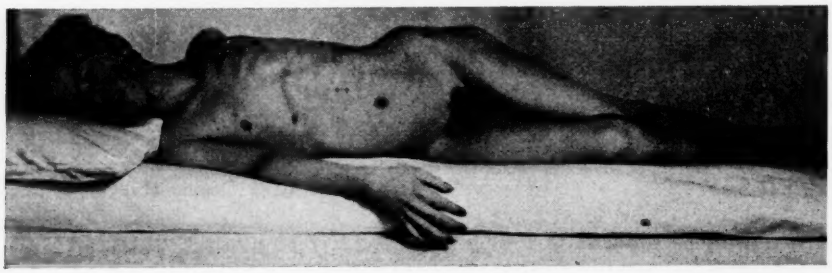

Fig. 1

Brousseau points to the insistence of most investigators that the female mongol exhibits no sexual activity and is unable to bear children. She was unable to verify reports of pregnancies in mongols. Pogue reported a married mongol who had had two conceptions. The first pregnancy was carried for 4 to 5 months, the second was full-term. Lind encountered in his series one pregnancy in which Cesarean section was performed. Unfortunately, little detail is given concerning the males, the age of the patients, or the kind of progeny, except that in Pogue's instance, the child was not a mongol. Church in discussing Pogue's paper thought the pregnancy significant and unusual in view of the mongols' backward genital development and incomplete sex differentiation. Benda was of the opinion that pregnancy in the mongol was practically impossible, stating that no authentic case had been reported. In a group of 10-year-old mongol girls, the ovaries showed degeneration of such marked degree that even the remote possibility of future function might be questioned.

CASE REPORT

A.B., a 13-year-old white male, was admitted to the hospital April 29, 1939, and died May 28, 1939. He had been diagnosed as a mongol soon after birth. Two weeks prior to this boy's admission, his brother, S.B., also a mongolian idiot, was found to have pulmonary tuberculosis. We were unable to obtain detailed data concerning the brother who, at the age of 14 years, was a patient in a State hospital. At this time he was of short, stocky build, with well developed genitalia. Secondary sex characteristics were present but no history was available as to the time of their appearance. A.B., had had measles, mumps and pneumonia. The father was 49 years of age, the mother 39 at the time of child's birth. At the present time there is only one living sibling, a girl of 27 years. The latter has two children, both apparently normal. An older sister who never menstruated, died of meningitis at the age of 12. Following the sister of 27, there were 3 other children. One, apparently normal, died of pneumonia at 2 years of age, the other 2 died in infancy. S.B. was next in line and after him the mother had one or two abortions and a miscarriage, following which A.B. was born. After A.B. the parents had one other child who died at birth. The sister stated that her mother had great difficulty with each delivery.

Physical examination revealed a mongolian idiot (fig. 1), height 51 in., weight 65½ lb. The pupils were round, equal and reacted to light. A convergent strabismus was present. The left disc was normal, the right disc margin was somewhat blurred. The heart and abdomen were normal. Subcrepitant rales were present in the left base posteriorly. There was no cervical rigidity. The reflexes including the Kernig, Babinski and Brudzinski were negative and marked flexibility of the extremities was present. The diagnosis of miliary tuberculosis was made. The child had a deep husky voice, a heavy growth of pubic hair, abundant hair on the upper lip, tufts of hair in each axilla, and recently chest hair had appeared. The penis was 7 cm. long in the unerected state, the circumference being 7.5 cm. The scrotum was 6 cm., the left testis 1.5 by 2.5 cm., the right 1.5 by 3 cm. Massage of the prostate and seminal vesicles yielded one fully formed but non-motile spermatozoan. From the sister we ascertained that A.B. had hair on his chin at 9 or 10 years of age and that pubic hair was noted at the age of 11. The penis had become enlarged about one year prior to admission but later she stated that his "transformation" really took place about one month before he became ill.

On admission the intracutaneous tuberclin test 1:1,000 was 2+ but it was negative when repeated on May 24. Sedimentation rate was increased. The blood count revealed a homoglobin of 11 gm., with 6,150 white blood cells. The differential included 79% polymorphonuclear leucocytes, 20% lymphocytes and 1% monocyte. The urine test results were entirely negative, as was also the Wassermann. Stomach washings failed to reveal any tubercle bacilli. Assay of the urine by the Zondek precipitation method demonstrated less than 66 M.U. (15).

A number of roentgenograms were taken. In each in-

stance both lung fields revealed diffuse flocculent, very fine infiltration, with fairly discrete, well circumscribed areas of opacity, diagnostic of miliary tuberculosis. No unusual findings were present in the long bones. There was some suggestion of smallness of the phalanges of the right fifth finger. The skull showed a slight increase in the digital markings. The sella turcica appeared to be normal in size and configuration; the clinoid processes were not eroded. The dorsal spine showed considerable scoliosis.

During the patient's course in the hospital the temperature ranged from 98° to 105° F. daily, until May 20, at which time the temperature remained persistently over 104° F. He developed difficulty in urination requiring catheterization. Soon the child developed neck rigidity, became comatose and expired. No autopsy was obtainable.

DISCUSSION

The question of the basophilic deficiency in mongolism is significant. If there is diminution or absence of basophils, then may we assume that this mirrors the hypogenitalism which mongols, with rare exceptions, usually exhibit? There is evidence that the basophilic cells are the particular ones in the anterior pituitary that form and store the gonadotropic hormone (16).

The marked genital development in our patient is difficult to explain. Our failure to obtain a necropsy leaves many questions unanswered, some of which, particularly those concerned with the status of the various endocrine glands, might have aided in clarifying the clinical picture the patient presented.

The question of hypergenitalism in children is interesting especially from the point of view of the number of situations, other than those arising in the endocrine glands per se, which may give rise to this picture (17). The question of an irritative tuberculous lesion or other growth in the area of the hypothalamus may be responsible for this picture. There is reason to believe that the hypothalamus either alone or in conjunction with the pituitary may play a role through the diencephalic pituitary mechanism in influencing certain fundamental functions, such as sexual development (18).

SUMMARY

A mongol with excessive genital development is reported. Attention is called to the possible relationship of basophilic deficiency and the hypogenitalism that mongolian idiots exhibit. (A necropsy was not obtained.)

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THYROID AND GROWTH

EFFECT OF THYROID HORMONE ON GROWTH IN THYROTOXIC AND MYXEDEMATOUS CHILDREN AND ADOLESCENTS

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INCREASE in length of an organism takes place in the early part of its life, and depends upon many factors. The harmonious relationship among these factors produces the normal and constant increase in length which is terminated when ossification is completed at the epiphyseal zones of growth. With the cessation of ossification and union of diaphyses and epiphyses the morphological and physiological maturity of the organism is usually reached.

The factors concerned with growth and maturity have been pointed out by many authors (1–11). It is difficult to establish a classification of these factors because there is complex interaction among them. This fundamental 'substrate,' by which is meant the inherent capacity of the cells of the organism to divide and produce new elements, has intrinsic characteristics due to hereditary factors which condition growth to a certain extent; and it is the 'substrate' upon which other factors operate.

Some factors, such as diet, may ultimately accomplish increase in mass by supplying the cells with the material necessary for their growth and division. Vitamins and hormones regulate cell metabolism and are responsible for growth and differentiation. We have to distinguish, therefore, between simple increase in mass such as can be produced by excessive diet and increase in mass resulting from growth and differentiation in which vitamins and hormones are involved.

Alteration of the capacity of the substrate can be illustrated clinically in cases of retardation of growth in the course of chronic disease. This interference with growth can be seen in the so-called zones of cessation of growth in the bones (12) and in the acceleration and retardation of ossification (13–17). The existence of a definite minimum effective dose and of a limit of maximum stimulation beyond which there is no further growth effect emphasizes the importance of the substrate.

The experiments of Smith (11) demonstrated a cessation of growth after hypophysectomy with resumption of growth following administration of active growth factor of anterior pituitary origin and a secondary cessation of growth on discontinuance of such treatment. Also, in accordance with the work of Smith, when thyroid is given together with pituitary growth hormone, growth is fostered more than by pituitary alone.

It is our purpose, in this paper, to show statural changes, in individuals of 20 years and under, clinically manifested as a function of the thyroid.

In the clinical field, the early descriptions of cretinism stressed the retardation of growth as an essential feature of the syndrome; and as time has passed, we have come to appreciate the relationship of failure of growth to thyroid deficiency. This explanation has been borne out further by the study of bone development in acquired hypothyroidism of the juvenile type in which it has been shown that there is retardation of epiphyseal closure and of development in the bones of the wrist.

The opposite phase of the question—namely, the possibility of clinical overgrowth as the result of hyperactivity of the thyroid—primarily concerns us in this study (18–23).

CLINICAL MATERIAL

We selected all the cases of definitely proved exophthalmic goiter in our juvenile group, that is all such patients of 20 years or under. There were 121 cases, 13 boys and 108 girls. For comparison we have inserted a few cases of juvenile hypothyroidism which we have had occasion to observe, 1 boy and 7 girls. From the 121 cases we exclude the boys for simplicity in graphic representation and 3 cases with independent chronic disease, thus leaving 104 cases with un-

Received for publication March 22, 1941.

complicated toxic goiter in girls. In figure 1 the height for age of this group is compared with that of normal girls; and it is apparent that the thyrotoxic are consistently taller for their age.

In figure 1 also is shown the average deviation from the normal height, in centimeters, of our juvenile patients with Graves' disease. (Benedict, Talbot and Crum-Wood tables were used to obtain normal average heights.)

It is clearly seen that up to the age of 18 when closure of epiphyses normally occurs and growth of normal individuals has usually ceased, as indicated by the plateau in the normal growth curve, there is a preponderance of over-height in hyperthyroid individuals.

From 18 to 20 years the tendency to over-height is less striking. Isolated examples of over-height in these latter age groups were investigated; and it was found that in these cases the disease had been present for a long time according to their histories, and at the onset of their illness the over-height individuals were in the 'open epiphyses' group. It is to be noted that the two maximum deviations in the hyperthyroid group coincide with the two normal accelerated growth periods, that is during the 6th to the 8th years and the 12th to the 14th years.

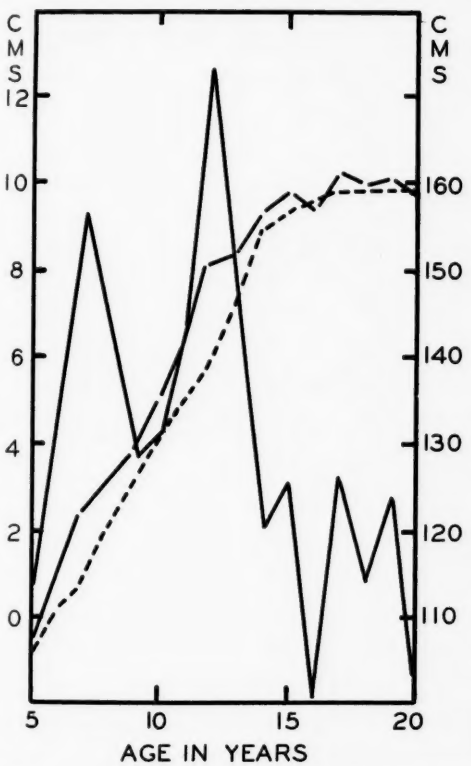


Fig. 1. Height referred to age for 104 thyrotoxic girls (broken line), compared with Talbot's curve for normal girls (dotted line). Scale on right. Average deviation in cm. of our juvenile patients with Graves' disease from normal height (solid line). Scale on left.

In considering excessive final stature we have to consider three different factors, any one of which may produce this condition.

(*a*) Growth at a normal rate, but prolonged beyond normal time limits (e.g., lack of inhibitory action of gonadal factors).

(*b*) Growth at an abnormally rapid rate for the normal period of time (acceleration of annual rate of growth, e.g., our group of thyrotoxic juveniles).

(*c*) Rapid rate of growth during an abnormally long period (e.g., pituitary overactivity in juvenile gigantism).

As indicated in figure 1, the cases of hyperthyroidism at the time of epiphyseal union, 18 to 20 years show no further excess in growth. This would indicate, as in the work of Smith, that the role of the thyroid is to speed up growth, but that the opposite processes, those that stop growth, take place at the correct time. Hence the largest deviations are observed in those cases in which the age of the patient allows the possibility of greatest growth.

In figures 2, 3 and 4 is represented, in reference to age, the growth of some of our patients. Normal growth is represented by heavy broken lines; and growth during the period of the disease of our patients is represented by dotted lines. The cross indicates the stature of the patients when first seen in the clinic; the arrow, the time when treatment was begun. The lower horizontal heavy line represents the normal rate of growth referred to the normal expected annual growth; the broken line represents, in centimeters, the excess over normally expected annual growth of the hyperthyroid patients. As can be seen in these graphs, the higher stature of the patients when first seen in the clinic indicates that previous growth has been acclerated as compared with the normal expected growth. When adequate treatment is given, the rate decreases, and comes to lie within normal limits. To compare, we show in figures 5, 6 and 7 the growth curves of 3 myxedematous patients with retarded rate of growth when first seen in the clinic, and accleration produced in them when treatment is given. The results are similar to those of other authors (38–41). They serve to stress the fact that thyroid feeding does not cause premature cessation of growth.

Dorothy B. (fig. 2) was admitted to the Massachusetts General Hospital at the age of 12 years, 10 months, with a classical picture of thyrotoxicosis of about 11 months' duration. Goiter, exophthalmus, weight loss of about 10 lb. were characteristically present. B.M.R. was between +50 and +60 before iodides were administered. Subtotal thyroidectomy was performed after a short preliminary period of observation on iodine. She was 11.8 cm. over-height for her age at the age of 12 years, this rapid rate of

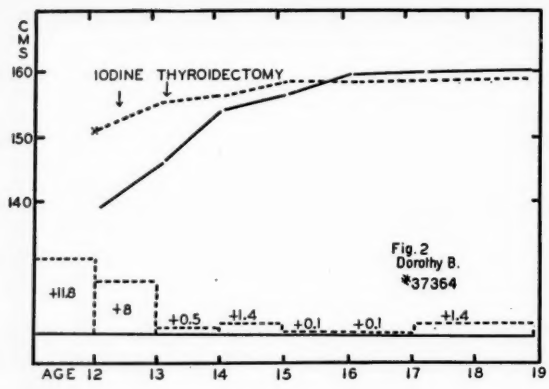


Fig. 2. GROWTH OF *Dorothy B.* IN CM. AT VARIOUS AGES DURING OBSERVATION ON IODINE AND AFTER SUBTOTAL THYROIDECTOMY (dotted line) AS COMPARED WITH AVERAGE NORMAL GROWTH CURVE (broken line). Below is given the deviation from annually expected growth during the same period, in cm.

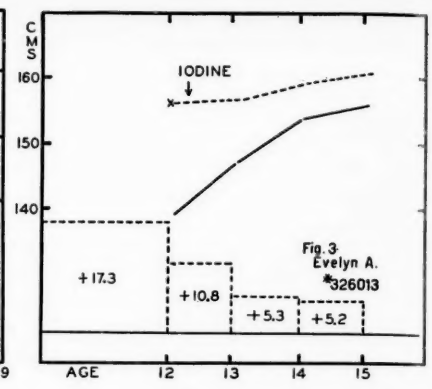


Fig. 3. GROWTH OF *Evelyn A.* IN CM. AT VARIOUS AGES DURING TREATMENT OF TYPICAL GRAVES' DISEASE.

growth continued while she was observed on iodine, and her growth approximated the normal after subtotal thyroidectomy.

Figure 3 shows the accelerated growth in *Evelyn A.* which occurred despite iodine treatment. This patient was 17.3 cm. overheight for her age at admission to the hospital at the age of 12.

Figure 5 shows the growth of *Dorothy M.* a myxedematous patient on thyroid therapy. Her chief complaint on admission was failure to grow. Characteristic facies of myxedema were present; and moderate obesity was associated with the other classic findings. B.M.R. was −25 to −32. Thyroid, 1.5 grains daily, was administered. Observation has continued in this case through the entire adolescent period. She was 12.2 cm. below average normal height at entry; and at the age of 17 was approximately 2 cm. overheight for her age. No evidence of premature closure of the epiphyses occurred in this case.

Florence McK. (fig. 6), aged 14, was 16 cm. underheight on admission. She was given 1.5 grains of U.S.P. thyroid daily. The growth rate approached normal thereafter.

Mary C. (fig. 7) was a typical case of myxedema at the age of 10½ years. Her primary complaint was failure to grow; she was 7.4 cm. underheight when started on thyroid therapy. In the next 3 years under thyroid therapy she grew 2.1 cm., 4 cm., and 2.8 cm. so that at the age of 13 she approximated normal height for her age.

DISCUSSION

We have shown in our material that an increase in height has to be included among the symptoms of thyrotoxicosis in young patients (17–23). The experimental work of Smith (11) indicates that the excess of thyroid is the basis of this acceleration of growth. Which comes first, the overgrowth of the individual or the hyperplastic state of the gland? Smith's work would indicate that the latter resulted in overgrowth because of the addition of extra thyroid hormone to the patient's normal production of growth hormone. Webster (37) would explain the acceleration of growth caused by thyroid as due to a stimulation of production of growth hormone, better utilization of foods, or some other, unknown mechanism. It is also conceivable that the thyroid hyperplasia is a result of increased growth and increased demand. Of our hyperthyroid patients 29 show an increase in stature that cannot be considered due to the disease, because the overgrowth could not have taken place during the short duration of the disease, or because the symptoms began when no further growth was expected, indicating that excess of growth had taken place before the onset of the disease. Such hyperplasia, however, does not occur in the cases of overgrowth due to gonadal insufficiency; the eunuchoidal type usually has a normal or lowered metabolism. These cases, in contrast to the above hyperthyroid cases, have to be included in the first type of overgrowth, that is, growth at a normal rate but over a longer period of time. There is no true acceleration of growth in these cases.

In the bibliography of juvenile thyrotoxicosis there is a considerable amount of literature (28) which summarizes the statistics. The cases presented in the last 10 years (24–36) do not give emphasis to stature as an important factor to be considered in determination of therapy.

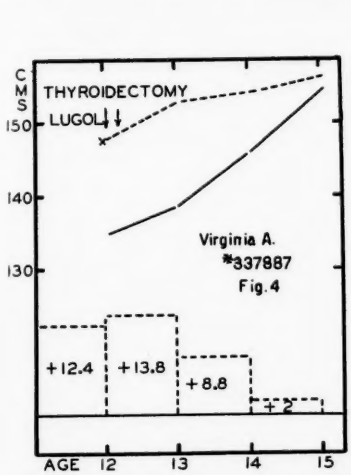
We would like to emphasize the importance of observing the two factors, actual stature and rate of growth of the young patients, in deciding as to whether the treatment should be more or less radical. A subject with a stature above normal, i.e., with a high rate of growth, should be submitted to a more

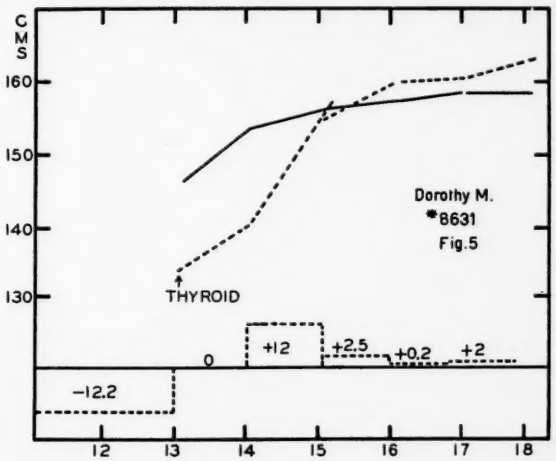
radical or more rapid cure than a subject with normal or lower than normal stature, whose disease it would be rational to treat with less interference with the growth stimulus, i.e. by non-surgical means, if other factors permit.

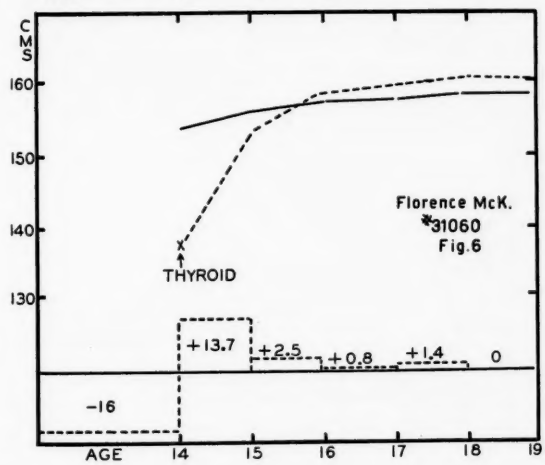
C. O. C. (*M. G. H. 245155*) was first seen in August of 1927 with a classic picture of Graves' disease in a boy of 14. Symptoms had been present for over 2 months. He was treated by the administration of Lugol's solution and given x-ray treatment, which improved his condition but did not cure it entirely. He grew 7 in. in the space of 22 months, and at the age of 28 (1940) presented the picture of 'thyrotoxic gigantism' shown in figure 8. According to our present knowledge of the relation of thyroid to growth we would (if we had this boy today) advise radical surgical treatment of his goiter because of the rapid speed of growth displayed during the period of partially uncontrolled thyrotoxicosis. This case illustrates most strikingly the fact that the excess of thyroid hormone did not produce an early or premature closure of the epiphyses. Had the latter occurred, gigantism would not have ensued. X-rays of the sella turcica of this boy were normal (1940).

SUMMARY

Factors governing the rate of growth of the human organism are discussed in relation to clinical evidence that the thyroid hormone is a synergist to the anterior pituitary hormone, which promotes growth. The animal experimental evidences of Smith are discussed in this connection. The growth promoting effect of thyroid therapy in juvenile myxedema is reviewed; and examples of such growth stimulation in our own clinic are cited. A study of the heights at various ages of 121 thyrotoxic patients in the juvenile







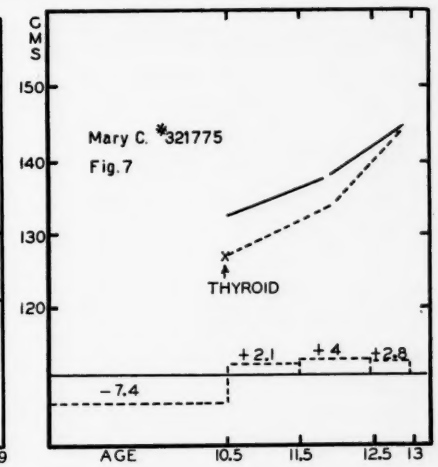


Fig. 4. Growth of *Virginia A.* at various ages during treatment of typical Graves' disease.
Fig. 6. Growth of *Florence McK.* Typical myxedema.

Fig. 5. Growth and annual statural increase of a patient with myxedema on thyroid therapy.
Fig. 7. Growth of *Mary C.* Typical myxedema.

group was made. Annual speed of growth was considered, as well as total growth as related to age and stage of treatment of the disease. The following conclusions were reached.

Fig. 8. An example of overgrowth due to uncontrolled thyrotoxicosis in a juvenile exophthalmic goiter patient. Acceleration of growth is due mainly to long bone stimulation.

Overgrowth takes place in juvenile thyrotoxic patients with such remarkable regularity that it can be considered one of the cardinal symptomatic manifestations of the disease in this age group. In our experience the speed of growth during the thyrotoxic period of individual cases is an even more striking feature than their actual degree of over-height for age. The excessive thyroid hormone present in such cases accentuates the peaks in the normal growth curves, and modifies the speed of growth according to the normally expected speed of growth at any given period of life of the juvenile patient with this disease. This is strikingly shown by the cessation of growth stimulation past the age of 16 years, at which time the epiphyses normally begin to close. It appears that thyroid hormone in excess does not produce premature or late closure of the epiphyses. Its growth effect can, therefore, be considered as truly synergistic to the normally existing factors for structural increase ('substrate').

A case of 'thyroid gigantism' in our clinic is presented as an example of the importance of applying the conclusions derived from this study in the clinical management of individual cases of juvenile thyrotoxicosis. In the determination of a therapeutic program for both the thyrotoxic and the myxedematous juvenile patient speed of growth must be regarded, as well as the actual height on presentation to the physician.

On the basis of this study we are at present studying the growth promoting effects of thyroid feeding on underheight individuals and pituitary dwarves.

We are indebted to Professor J. H. Means, Chief of the Medical Staff of the Massachusetts General Hospital, for valuable advice and stimulation in the course of this work.

Aid was given in the completion of this work from the Proctor Fund, Harvard Medical School, Harvard University, and the H. N. C. Fund for Medical and Surgical Research.

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CLINICAL STUDIES OF THYRO-GONADAL CORRELATES: I. BASAL METABOLIC RATES AND ENDOMETRIAL RESPONSES[1]

THYRO-GONADAL INTERRELATIONSHIPS

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AMPLE CLINICAL DATA exist to justify the belief that there are intimate relationships between the functions of the thyroid and ovaries in producing the physiologic phenomena and pathologic aberrations of the gynecic sexual system. Few clinical studies have been made of the nature and extent of these interrelationships. Most clinical reports deal with the therapeutic applications of thyroid substance in gynecic practice and give few factual data on the endocrine mechanisms of the functional disturbances treated or of the *modus operandi* of the therapeutic agent employed. Because of these facts, and ones equally true for the male, a comprehensive program of clinical study of thyro-gonadal associations has been initiated. The present report deals with correlational data secured from basal metabolic determinations and from studies of endometrial specimens secured by biopsies.

Experimental and Clinical Data Regarding the Mechanisms of Thyro-Gonadal Interrelationships

Various recent reviews upon the subjects of thyro-gonadal and thyro-gonado-pituitary interrelationships have led to diverse conclusions. Severinghaus (1) has observed that thyroid participation in gonado-pituitary relations seems evident and that disturbances in thyroid function alter the structure of the anterior lobe of the pituitary. Thyroidectomy eliminates the acidophils in some species, while basophils are augmented and basophilic vacuolization ('thyroidectomy cells') develops. In hyperthyroidism, however, both the acidophils and basophils appear to be augmented.

Van Dyke (2) has concluded that thyroid activity is probably of no great significance in the regulation of gonadal function, its usual effect, if any, being to lessen the follicle stimulating activity of the pituitary.

Moore (3) has expressed the opinion that experimental data have not established the existence of any direct relationship between the thyroid and testes and that there is good evidence, however, of the occurrence of indirect functional associations, which are mediated by way of alterations in oxygen metabolism.

Salter (4), on the other hand, has suggested 3 possible types of thyro-gonadal reciprocities: 1) a 'peripheral sensitization' of tissues to the gonadal hormones by the thyroid[2]; 2) effects produced by thyroid activity upon the gonado-pituitary axis, or vice versa; and 3) indirect effects of the thyroid upon the gonads by way of alterations produced in glands other than the pituitary, i.e., the adrenals. Some workers (6), however, calling attention to the importance of the sex sterols, estrogens in particular, in general hormonal regulation, have suggested that the gonads may play an important role in the regulation of thyroid function. Thus the commonly observed and frequently described associations of thyroid and gonadal aberrations may be viewed from the standpoint of thyroid primacy or of gonadal primacy or a reversible two-way reciprocity may be envisioned.

Received for publication March 10, 1941.
[1] These studies were aided by grants from the Research Council of Duke University and from Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

[2] The experimental studies of Tyndale and Levin (5) add weight to this point of view. They relate the primary influence of the thyroid upon gonadal function to a peripheral reactivity phenomenon rather than to one mediated by way of the pituitary.

Experimental data upon the gonadotropic contents of the pituitaries of animals with disturbed thyroid function, as reviewed by Severinghaus (1), are contradictory. Different observers have described varying findings: increased gonadotropic potency of the pituitary of the hyperthyroid rat (Cohen, Evans and Simpson, Van Horn); no alteration in the gonadotropic content in hypothyroid or hyperthyroid rat (Smelser); no alteration in the hypothyroid rat (Smith and Engle, Van Horn); decreased gonadotropic content in the hypothyroid rat (Evans and Simpson). Severinghaus attributed these discordant findings to the greatly disturbed balance between acidophils and basophils which characterizes thyroid aberrations as well as to the failure of the various workers to employ methods of gonadotropic assay capable of segregating qualitative as well as quantitative alterations in these functions of the pituitary.

Studies of the functional status of the gonads of experimental animals with induced disturbances of the thyroid have not yielded consistent data. Moore (3) has observed that disordered thyroid functions, as a rule, impair spermatogenesis, although some animals appear to be singularly independent of the thyroid influences in this regard, i.e., the frog tadpole (Allen) and the immature rat (Ross). Smelser, quoted by Severinghaus (1), demonstrated, however, that hyperthyroid rats suffered testicular weight loss and regressional alterations in the accessory organs of the same order as castrated animals. These alterations were prevented when injections of gonadotropins were given. Weichert and Boyd, also quoted by Severinghaus (1), however, observed that hyperthyroid female rats have persistent corpora lutea in their ovaries. Severinghaus, citing this last work and calling attention to the fact that hyperthyroidism is associated frequently with acromegaly and pregnancy, expressed the belief that the cytologically active acidophils of the pituitary were related to thyroid as well as to gonadal function.

Pertinent clinical data upon thyro-gonadal interrelationships are exceedingly meager. Severinghaus (1) has reported that MacCallum and Fabyan, Schultze, Wegelin, and Vryman found acidophils decreased in the pituitaries of patients with thyroid deficiency. Howell (7) found increased gonadotropic titers of the urines of patients of both sexes with disturbed thyroid function, regardless of its nature.

The majority of recent clinical reports (8) deals with the incidence of menstrual irregularities, sterility and abortion in thyroid diseases and with the effectiveness of appropriate therapies. Significant detailed studies of the functional status of gonads before and after treatment for thyroid diseases have not been encountered. Howard (9) stated that genital hypoplasia is not infrequent in hyperthyroidism but that no characteristic changes occur in the gonads. It may be assumed that the gonadal failure of advanced hyperthyroidism is due to a large extent to the effects of the concomitant cachexia upon the pituitary-gonad axis. Retardation in sexual maturation is observed frequently in association with childhood hypothyroidism and cretinism. Howard (9), observing that complete impotence is the rule in cretinism, quoted Langhans as having reported that the testes and epididymes of a 24-year-old cretin were of 'child-like size' and that spermatozoa were absent or markedly decreased in numbers. Clinical observations, however, indicate that sterility is not necessarily the rule with moderate or even severe hypothyroidism. Rolleston (10) stated that myxedema in men may not impair fertility. Marañon (11) reported the occurrence of gynecomastia in 2 hyperthyroid males.

Various theories as to the mechanisms of thyro-gonadal interrelationships may be summarized as follows.

(1) The level of thyroid function influences the gonado-pituitary axis through the possible common acidophil origin of luteinizing gonadotropin and thyrotropin:

- (a) Indirectly, by alterations in thyrotropic functions, which result in sympathetic disturbances in gonadotropic activities;
- (b) Directly, by immediate effects on gonadotropic levels;
- (c) Indirectly, due to an immediate thyro-gonadal relationship which results in alterations of gonadotropic levels secondary to fluctuations in gonadal sterols.

(2) A direct thyro-gonadal relationship exists whereby thyroid levels alter gonadal function by local metabolic or sensitization effects.

(3) An indirect thyro-gonadal association may exist through the medium of the adrenal glands.

(4) Gonadal function may be the primary factor in thyro-gonadal relationships, exerting by way of the gonadal sterols important influences upon thyroid function, either directly or by way of the gonado-thyro-pituitary axis.

METHODS

A group of 179 women, whose ages ranged from 13 to 45 years, was studied. This group was selected from consecutive patients seen and studied in the Endocrine Division during the past several years. All of these patients had received routine endocrines, medical and gynecologic surveys as part of the study of their chief complaints: irregular uterine bleeding, dysmenorrhea or sterility. All had had one or more pretreatment determinations of basal metabolic rate and one or more endometrial biopsies.

Basal metabolic rates were determined routinely by trained technicians of the Metabolism Division. The Benedict-Roth apparatus was used. All patients

TABLE 1. ONE HUNDRED AND ELEVEN PATIENTS WITHIN THE NORMAL B.M.R. RANGE

Menstrual History	Patients	Age		B.M.R.		Hypoestrogenic	Persistent estrogenic	Hyperestrogenic	Total estrogenic	Mixed progestational	Progestational	Total progestational
		Range	Average	Range	Average							
Polymenorrhea	14	14–31	23.5	−7 to +10	+0.1		3	2	5	2	7	9
Hypomenorrhea	4	20–37	31.0	−9 to +10	−2.5		2		2	1	1	2
Oligomenorrhea	12	17–30	22.8	−10 to +10	−1.2	2	5	2	9	3		3
Hypermenorrhea	4	28–37	31.2	−3 to +6	+3.0					4		4
Menometrorrhagia	47	13–37	24.3	−10 to +10	−0.3		21	10	31	15	1	16
Amenorrhea	10	17–30	23.4	−9 to +7	−0.9	5	4		9	1		1
Dysmenorrhea	6	17–29	22.8	−10 to 0	−2.6		1		1	3	2	5
Sterility (cyclic bleeding)	14	20–34	25.1	−9 to +10	−3.0		2		2	6	6	12
Totals	111					7	38	14	59	35	17	52

were ambulant. Routine enforced at least 12 hours of fasting and 30 minutes of bed rest immediately prior to examination. All tests were made during the morning hours after an adequate night's rest. Calculations were based upon the Dubois body surface chart, as modified by Boothby and Sandiford. Normal rates were assumed to be represented by values ranging from +10% to −10%.

Since studies of blood cholesterol and of creatine metabolism are not employed by us as routine diagnostic measures in the endocrine surveys of all patients seen, data on these are not available for this group of patients. (This group of patients obviously is not comprised of patients selected for special research and submitted to an organized plan of special studies.)

Endometrial biopsies were secured within 12 to 18 hours after the onset of episodes of uterine bleeding. At such biopsy bits of endometrium were taken from 3 different sites of the uterine mucosa. After the usual fixing, mounting and staining of the tissue with hematoxylin and eosin, microscopic studies were made by one of us (E.C.H.) and the endometrial pattern was classified according to a system described previously by one of us (12). In the event bleeding was found to occur from estrogenic endometria (i.e., was presumed to have been anovulatory), at least 2 or 3 consecutive episodes of flowing were sampled by endometrial biopsy in order to establish the fact that estrogenic bleeding was habitual for the patient.

Symptoms, other than those comprising the chief complaints, and significant physical signs are not reported in this study. The majority of patients with basal metabolic rates lower than −15% presented symptoms and clinical findings associated with hypothyroidism.

DATA

For the presentation and analysis of data the 179 patients are divided into 2 groups: those whose basal metabolic rates ranged from +10% to −10%; and those whose basal metabolic rates were less than −10%. Tables 1 and 2 present the significant clinical data regarding these two groups of patients.

For comparison with these data and for the purpose of delineating more clearly the effects of hypometabolism on ovarian function, table 3 gives a summary of the endometrial findings of patients with basal metabolic rates which were less than −15%.

In order that a direct comparison might be made between the endometrial and metabolic data of tables 1 and 2 and the endometrial data previously reported

TABLE 2. SIXTY-EIGHT PATIENTS WITH B.M.R. VALUES LESS THAN −10%

Menstrual History	Patients	Age		B.M.R.		Hypoestrogenic	Persistent estrogenic	Hyperestrogenic	Total estrogenic	Mixed progestational	Progestational	Total progestational
		Range	Average	Range	Average							
Oligomenorrhea	8	16–30	22.7	−11 to −18	−13.1		5		5	3		3
Hypermenorrhea	2	31–42	36.5	−11 to −12	−11.5					1	1	2
Polymenorrhea	12	14–37	26.3	−11 to −18	−13.1		1		1	9	2	11
Amenorrhea	4	18–31	23.7	−12 to −18	−13.5	1	2		3	1		1
Hypomenorrhea	2	26–32	29.0	−12 to −16	−14.0		1		1		1	1
Menometrorrhagia	24	13–45	24.2	−11 to −27	−13.0		10	9	19	3	2	5
Dysmenorrhea	2	30–33	31.5	−17 to −22	−19.5		1		1	1		1
Sterility (cyclic bleeding)	14	24–37	31.4	−11 to −27	−13.5		3		3	7	4	11
Total	68					1	23	9	33	25	10	35

by one of us (13) on patients with functional irregularities of uterine bleeding in whom no segregation of thyroid factors was made, table 4 is presented. In this table the two groups of patients presented in tables 1 and 2 are modified by the subtraction of patients with regular bleeding (those with sterility and dysmenorrhea) in order to make the 3 groups similar, that is, composed of patients with irregular bleeding.

Table 5 contains a summary of the preponderant menstrual symptoms of the patients of tables 1 and 2.

DISCUSSION

These clinical data do not indicate that hypothyroidism has any constant role in the pathogenesis of qualitative endocrine failure of the ovaries. There occurs no higher incidence of estrogenic bleeding (presumed anovulatory bleeding) among the patients with basal metabolic rates of less than -10% than among those whose basal metabolic rates fall within the limits, accepted to be normal: $+10\%$ to -10%. The most striking data are those obtained from regrouping the patients with decreased metabolic rates so that those with rates less than -15% (and in this particular instance as low as -27%) are evaluated as regards endometrial responses. When this group is considered there is almost a 2-fold increase in the incidence of progestational bleeding. Reference to table 3 confirms the statement that patients with some of the lowest basal metabolic rates bled from progestational endometria. All of these patients presented amply acceptable evidence of hypothyroidism to permit significant generalizations regarding thyrogonadal interrelationships.

It is obvious that these data do not permit the all-inclusive statement that thyroid failure produces no alterations in the endocrine function of the ovaries. The method for sampling ovarian function in this study supplies direct evidence only as regards the occurrence or non-occurrence of corpus luteum function. It has been clinical practice to interpret these observations as signifying the occurrence or non-occurrence of ovulation. Significant fluctuations in the secretion of estrogens and of progesterone by the ovaries, if they occur in hypothyroidism, would not be identifiable by endometrial data unless these fluctuations were of sufficient magnitude to be associated with the non-occurrence of ovulation and corpus luteum proliferation. Likewise minor variations in the length or level of corpus luteum activity would not be identified by the endometrial method of evaluating ovarian function. Detailed correlational studies of hormonal titers of body fluids and endometrial responses of hypothyroid patients as compared with non-hypothyroid women would be necessary for information of this nature.

There are two other effects of hypothyroidism upon ovarian function to the occurrence of which clinical practice attests: disturbed cyclicity of bleeding and sterility. The irregular bleeding may be regarded as due to quantitative rather than qualitative alterations in ovarian function: the hypometabolism results in a 'slowing down' of ovarian activity, in common with similar effects upon all other physiologic processes but this does preclude the likelihood that complete ovarian cycles may occur although at infrequent intervals, that is, oligomenorrhea and amenorrhea. The commonly encountered sterility of hypothyroid patients may be referred directly to this

TABLE 3. ENDOMETRIAL CORRELATES OF 15 PATIENTS WITH B.M.R. VALUES LESS THAN -15%

B.M.R.	Age	Estrogenic	Progestational
−16	24		1
	32		1
	29		1
	33		1
−17	14	1	
	19		1
	26		1
	33	1	
−18	23	1	
	24		1
	26	1	
	35		1
−22	30		1
−27	35	1	
	45		1
Totals		5	10

TABLE 4. ENDOMETRIAL CORRELATES OF PATIENTS WITH FUNCTIONAL UTERINE BLEEDING SELECTED FROM THE NORMAL B.M.R. GROUP, THE LOW B.M.R. GROUP, AND SERIES II OF A PREVIOUSLY REPORTED GROUP[1]

	Normal B.M.R.		Low B.M.R.		Series II of previous group[1]	
	No.	%	No.	%	No.	%
Total estrogenic	56	61.5	29	55.7	83	64.3
Total progestational	35	38.4	23	44.2	46	35.7

[1] HAMBLEN, E. C.: *Sou. M. J.* 32: 308. 1939.

TABLE 5. SUMMARY OF THE MOST FREQUENTLY OCCURRING MENSTRUAL SYMPTOMS OF THE NORMAL AND THE LOW B.M.R. GROUPS

Normal B.M.R. values	Low B.M.R. values
Hypomenorrhea	Polymenorrhea
Hypermenorrhea	Oligomenorrhea
Menometrorrhagia	Sterility (cyclic bleeding)
Amenorrhea	
Dysmenorrhea	

'slowing down' of ovarian activity or to the damaging effects of hypometabolism upon the germinal elements (gametopathic effects of lowered oxygen metabolism); our data do not warrant its assignment to the non-occurrence of ovulation. The high incidence of abortion in hypothyroidism favors the gametopathic viewpoint.

Regarding the nature of the thyro-gonadal interrelationships, the clinical data presented in this communication do not appear to justify the theory of an active participation by the thyroid in the gonado-pituitary axis. It seems more likely that the thyroid influence upon the ovary is secondary and is mediated by changes in the local oxygen metabolism of ovary which doubtlessly determine to a great degree its 'responsiveness' or 'sensitivity' to gonadotropic influences. When the ovary responds to these influences, it usually appears to give a qualitatively normal endocrine one in hypothyroidism.

SUMMARY

Correlational studies of basal metabolic rates and endometrial responses are reported upon a series of 179 women who were studied because of irregular uterine bleeding, dysmenorrhea or sterility. Patients whose basal metabolic rates were less than −15% and whose other clinical symptoms and signs justified the diagnosis of hypothyroidism had significantly less qualitative disturbance of ovarian function, i.e., bled more frequently from progestational endometria, than those patients with normal metabolic rates. These studies are judged to warrant the assumption that the thyroid has no direct association with the gonado-pituitary axis. It is suggested that the hypometabolism of thyroid failure results in a quantitative 'slowing down' of ovarian activity (without qualitative alterations in the responses given) and in faulty maturation of ova (gametopathic failure): alterations in the local oxygen metabolism of the ovary are concerned to a great degree with its 'responsiveness' or 'sensitivity' to the gonadotropic influences of the pituitary.

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THYRO-GONADAL INTERRELATIONSHIPS

CLINICAL STUDIES OF THYRO-GONADAL CORRELATES. II. BASAL METABOLIC RATES AND SEMINAL FINDINGS[1]

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THE PRELIMINARY CONSIDERATIONS of the preceding article have set forth the advisability of studying the thyro-gonadal interrelationships in the male. Both the endocrine and exocrine (gametokinetic) functions of the male gonads merit investigation under the conditions of varying grades of thyroid activity. The present study deals with correlations of basal metabolic rates and seminal biometry and cytology.

At the present, any investigations of spermatogenic functions to a great degree are unsatisfactory because of our deficient knowledge of the normal physiology of spermatozoa. Hartman's recent review (1) takes critical inventory of this knowledge. While fairly well accepted standards of normalcy are recognized for numbers and dilution of spermatozoa, cytologic characteristics, degree of and duration of motility of spermatozoa and volumes of ejaculates, there is little critical information upon the various factors which may influence these. Segregation of single causal variants in comparative studies of seminal specimens is necessary and yet, at present, this is always uncertain due to the inadequate synthesis of our knowledge of male reproductive physiology. Among some of the factors to be considered are: the environmental conditions which influence spermatozoa, including PH, ionic concentrations, temperature, tissue extracts, oxygen and carbon dioxide levels, radiant energy and fluids used for dilution; relationship between fertilizing ability and commonly studied biometric and cytologic data; inadequacy of methods for evaluating germinal adequacy; the various facets in maturation and aging of spermatozoa in the genital tract; the relationship between spermatozoal storage, aging and dissolution as these influence interpretation of continence; the choice of time for securing seminal specimens for examination as determined by varying data on the effects of repeated ejaculations and continence.

While experimental studies have suggested for the follicle stimulating gonadotropin of the anterior pituitary the primary endocrine role in regulating the activity of the seminal epithelium, there are reasons to believe that other glands may exert important influences upon spermatogenesis. Walsh, Cuyler and McCullagh (2) in 1934 showed that injections of androgens were capable of preventing the usual post-hypophysectomy testicular atrophy in rats, thereby permitting continued spermatogenesis; these observations have been confirmed repeatedly by subsequent workers. Clinical practice has found the use of thyroid substance frequently effective in lowered fertility of the male. The theoretical mechanisms of thyro-gonadal relationships have been summarized in the preceding article.

A search of the clinical literature has yielded few significant data upon correlational studies pertinent to this relationship. Some important clinical generalizations have been encountered. Moench (3) has stated: "It seems significant to me that practically every single man with disturbed spermatogenesis has had a basal metabolism at least somewhat below normal. I feel that even slightly lowered thyroid function should be corrected, and have the impression that the

Received for publication March 10, 1941.
[1] These studies were aided by grants from the Research Council of Duke University and from Ayerst, McKenna & Harrison, Ltd., Montreal, Canada.

amount of good which can be accomplished by thyroid therapy is not expressed entirely by the figure obtained by the basal metabolism test."

Kreutzmann (4) has referred without giving specific details to a group of 48 men studied by him. He classified the seminal findings of these patients into 4 groups:

1) Normal sperm count and normal percentage of abnormal forms with a lowered basal metabolic rate.
2) Oligospermia and a normal percentage of healthy sperm.
3) Normal number of sperm with an increase in abnormal forms.
4) Oligospermia with an increase of abnormal forms.

He stated that "fifteen per cent of the patients were in *group* 1, having a basal rate varying from minus 10 to 18. They were all given thyroid by mouth following which the desired results were obtained."

Meaker and Vose (5) have observed: "The hypothyroid cases, which are fairly numerous, form an interesting group. Often these patients present none of the classic signs or symptoms of myxedema; a diagnosis can be made only on the basis of metabolic rate and other laboratory measurements. The semen in general is good, except for a slight increase in the incidence of abnormal morphology. In other words, the fundamental trouble in such a case is so little evident that it would rarely be discovered without complete diagnostic study. But successes following thyroid treatment are now numerous enough to remove all doubt about the cause and effect relationship of that trouble to infertility."

Charny (6) has stated that both hyperthyroidism and hypothyroidism may cause oligospermia, even though the thyroid disturbances are not severe ones.

METHODS

A group of 53 male partners of couples being surveyed in the Endocrine Division because of sterility supplied the data for these studies. The ages of these patients ranged from 26 to 47 years. While these patients were chosen consecutively, they were selected from a much larger group, all members of which were not suitable for the present study. There were selected only males who had no therapy, who had no mechanical blockage of the ductular system and who had had several complete seminal studies and one or more determinations of basal metabolic rates. As this group did not constitute one selected in advance for an organized plan of research but rather one comprised of patients who had undergone routine studies, no data are available as to special studies of thyroid function, such as creatine metabolism, blood cholesterol, etc. All patients had received medical, urologic and endocrine surveys as part of their examinations. The significant findings disclosed by these surveys except those related to basal metabolism and seminal specimens are not considered in this study.

Determinations of basal metabolic rates were carried out as described in the preceding article. Rates ranging from +10% to −10% were considered normal.

With a few exceptions, seminal specimens were obtained only after continence of 5 to 7 days' duration. All specimens were secured by masturbation and were examined promptly. Our technic of seminal evaluation has been described in detail (7); it is essentially that employed by Meaker and his group (8). Observations made, together with the criteria accepted for normalcy, included: volume, 3 to 4 cc.; degree of motility of spermatozoa, 80 to 100%; number of spermatozoa, 200,000,000 to 60,000,000 per cc. of ejaculate; incidence of abnormal cytologic forms, less than 20%; degree of motility of spermatozoa after exposure to room temperature for 24 hours, no finite limits; generally it is stated that spermatozoa of healthy men remain motile under these circumstances. The lower limit of normal counts was accepted to be that of 60,000,000 spermatozoa per cc. and 240,000,000 for the entire ejaculate.

DATA

In order to avoid undue complexities and conserve space, the detailed findings of each of the 53 patients are not presented. Instead, the ranges and averages of the results of each different observation of groups of these patients rather than those of the individual

TABLE 1. COMPARATIVE DATA FROM SEMINAL EXAMINATIONS OF 53 PATIENTS WITH NORMAL AND LOW B.M.R. VALUES

	No. patients	B.M.R. range	Normal seminal findings		Abnormal seminal findings					
					Total abnormal seminal findings		Abnormal counts		Abnormal morphology	
			Patients	%	No. patients	%	No. patients	%	No. patients	%
Group 1.	27	−10 to +10	3	11.2	24	88.8	14	51.8	17	62.9
Group 2.	13	−11 to −15	1	7.7	12	92.3	4	30.7	11	84.6
Group 3.	13	−16 to −21	3	23.1	10	76.9	4	30.7	7	53.8
Totals	53		7		46		22		35	

patient are given. The patients are grouped according to values of their basal metabolic rates: *group 1*, patients with basal metabolic rates ranging from +10% to −10%; *group 2*, patients with basal metabolic rates ranging from −11% to −15%; *group 3*, patients with basal metabolic rates of −16% or lower.

Table 1 presents an analysis of these 3 groups according to the incidence of normal or abnormal semen, as judged by the generally accepted criteria and also segregates the incidence of decreased spermatozoal counts and of increased abnormal cytology.

Table 2 gives an analysis of the 3 groups of patients upon the basis of ranges and averages of the findings which resulted from the observations made upon seminal studies.

Table 3 segregates the data secured from seminal studies upon those patients of *groups 1* to 3 who had testicular hypoplasia or atrophy.

TABLE 2. COMPARATIVE DATA FROM SEMINAL EXAMINATIONS OF 53 PATIENTS WITH NORMAL AND LOW B.M.R. VALUES

	Group 1 (B.M.R. −10 to +10%)	*Group 2* (B.M.R. −11 to −15%)	*Group 3* (B.M.R. −16 to −21%)
Motility			
Immediate			
Range	0–95%	0–95%	0–95%
Average	39.1%	42.9%	71.3%
Endurance (24 hours—Room temperature)			
Range	0–50%	0–50%	0–70%
Average	8.2%	14.4%	28.2%
Biometry			
Volume			
Range	1.0–12.0 cc.	1.0–6.0 cc.	0.5–5.5 cc.
Average	4.7 cc.	3.8 cc.	2.9 cc.
Count per cc. (Expressed in millions)			
Range	0–210	2–215	0–200
Average	66	60	66
% below the mean	85.1%	84.6%	69.2%
Cytology—Abnormal forms			
Range	10–85%	20–80%	18–50%
Average	44.5%	44.0%	28.9%

DISCUSSION

These studies do not indicate that deficiency of thyroid function exerts any constant or specific influences upon the commonly studied biologic properties of spermatozoa. Those patients whose basal metabolic rates were less than −10% showed no higher incidence of inadequate semen than those whose basal metabolic rates were normal. As a matter of fact, there was a higher incidence of normal seminal findings in *group 3* (patients with basal metabolic rates less than −15%) than in either of the other two groups: this incidence was twice that of the patients with normal basal metabolic rates.

In the preceding article, we were able to show that no significant qualitative alterations in the endocrine function of the ovaries were produced by hypothyroidism. We suggested that the *modus operandi* of thyroid deficiency in producing ovarian sterility was probably due to the damaging effects of the associated decreased oxygen metabolism upon the germ plasm of the ova or upon the process of oögenesis. In the present study, which is concerned with the gametogenic function of the male, we anticipated the likelihood of being able to segregate the nature of the gametopathic effect exerted by hypothyroidism. We expected to find a characteristic impairment of motility or endurance of spermatozoa or a significant increase in abnormal forms of these. None of these expectations was borne out by this study. As a matter of fact, the opposite findings were encountered: the spermatozoa of hypothyroid patients (*group 3*) showed greater motility and fewer abnormal forms than patients with normal basal metabolic rates (*group 1*) or with moderately decreased basal metabolic rates (*group 2*).

In view of the fact that clinical experience is just as convincing in the instance of endocrine sterility of the male, as in that of the female, as to the therapeutic value of thyroid substance, even when no marked depressions in basal metabolic rates occur, we must continue to accept the existence of a cause and effect relationship between thyroid deficiency and seminal inadequacy. These studies bring into clear relief the apparent shortcomings of our present methods for seminal evaluation in regard to identifying the game-

TABLE 3. COMPARATIVE DATA OF SEMINAL STUDIES OF 10 PATIENTS WITH NORMAL AND LOW B.M.R. VALUES PRESENTING DECREASED TESTICULAR VOLUME

	Group 1 (B.M.R. −10 to +10%) 5 Patients	*Group 2* (B.M.R. −11 to −15%) 1 Patient	*Group 3* (B.M.R. −16 to −21%) 4 Patients
Motility			
Immediate			
Range	5–60%	—	25–75%
Average	31.6%	0.0%	37.0%
Endurance (24 hours—Room temperature)			
Range	0–10%	—	0–12%
Average	3.3%	—	6.0%
Biometry			
Volume			
Range	2.5–6.0 cc.	—	0.5–4.0 cc.
Average	4.6 cc.	1.0 cc.	1.8 cc.
Count per cc. (Expressed in millions)			
Range	0–25	—	0–130
Average	6.4	42.5	32.5
% below the mean	80.0%	—	50.0%

topathic effects of hypothyroidism. These may be related to a deficiency in the fertilizing power of spermatozoa, which function cannot be related to assessments of motility alone or this influence may be one exerted upon the germ plasm itself, the inadequacy of which cannot be gauged by our present methods. Amplication of these methods is highly desirable if significant data are to be secured.

These studies, while not permitting an unequivocal statement of fact, suggest the possibility that in the male as in the female the principal thyro-gonadal relationship is not by way of the gonado-pituitary axis but probably by way of direct effects of alterations in oxygen metabolism upon the physiology of, and in particular the 'sensitivity' and 'reactivity' of, the germinal epithelium.

SUMMARY

Correlational studies of basal metabolic rates and biometric and cytologic data from seminal studies are reported upon a series of 53 males who received routine studies because of presumed sterility. Commonly employed methods for assessment of seminal adequacy failed to segregate any specific impairment which could be related to the hypothyroidism. Patients whose basal metabolic rates were less than -15% yielded better seminal specimens, as judged by the generally accepted criteria, than those patients with normal basal metabolic rates. These studies indicate the apparent necessity for better methods of seminal evaluation, especially in regard to the fertilizing ability of spermatozoa and the condition of the germinal plasm. No evidence was obtained that the thyroid has any direct participation in the gonado-pituitary axis.

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UMBILICAL HERNIA OF INFANTILE MYXEDEMA

HYPOTHYROIDISM

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AMONG the many symptoms and signs of congenital or early infantile myxedema, and described many years ago, is umbilical hernia. Its reduction or even complete disappearance, solely from the administration of thyroid substance, is demonstrated clearly in the accompanying photographs of the following cases.

Case 1, M. M. (University of California Hospital, O. P. D., No. *U* 53747). This girl was normally delivered at term. Her mother was not thought to have suffered from any iodine deficiency, metabolic disturbance or endocrinopathy. The pregnancy and birth occurred in a region where goiter is not endemic and the child was reared there. Her birth weight was 9 lb., 10 oz.; her length 20 in.

The parents sought medical advice when the patient was 9 months old, principally because of failure to grow properly, the length increment having been but 2½ in. in 9 months. The average growth expectancy during this period is about 6 to 7 inches. Despite a poor appetite her weight was 13¼ lb., 2½ lb. more than the ideal weight for her length. Other complaints mentioned by the parents were an annoying constipation, inability to hold her head erect, lack of attention to her surroundings, frequent crying but no other sounds, and restless sleep.

The patient's facies (fig. 1) resembled a bulldog's, with puffy bloated features; her tongue was large and thick, her voice rough and low-pitched. Her complexion was pale, the skin of her arms and legs felt cold and was thick, dry and slightly scaly. When placed in the sitting posture lumbar kyphosis was very noticeable. The abdomen was prominently protuberant with a conspicuous umbilical hernia admitting the tip of the small finger (fig. 2). Physical and mental activity was definitely retarded and estimated at 3 months (6 months retardation).

Study of the blood revealed an hypochromic microcytic anemia; a lipemia although the cholesterol fractions were normal; a low iodine content (2.1 micra%) (4–6 micra considered normal); Wassermann test result was negative. Urine examination results were negative. Bone age as shown by x-ray was estimated at not over 4 to 5 months, a retardation of 4 to 5 months. The kyphosis was explained partly by roentgenograms of the spine which showed that the superior halves of the upper three lumbar vertebrae had not developed in proportion to the lower halves. An electrocardiogram showed a tendency toward right axis deviation, low voltage, prominent Q_3, abnormal contours of the T_1, T_2 and T_3 waves with variable degree of inversion. The B.M.R. (estimated from the insensible perspiration) was −45%.

When the child was 9½ months of age, thyroid substance was started with a dosage of 1/10 grain 3 times daily. She grew 1.4 in. in the succeeding 6 weeks, was noticeably more animated and more active physically, tried to form words and was holding her head erect. The face was less puffy and the eyes brighter, the tongue smaller, the hair softer, the skin smoother and warmer, the voice higher pitched (fig. 3). She was not constipated. The abdomen was far less protuberant and the umbilical hernia had practically disappeared. This transformation over a period of only 6 weeks was most impressive.

Other manifestations of improvement included less anemia, reduction of the cholesterol level and a more nearly normal electrocardiogram.

The daily dose of thyroid substance was then increased from 3/10 grains to ¾ grains.

The baby was able to sit up by herself at 13½ months of age; she stood up with support at 14 months and attempted to walk at 14¼ months. The first tooth did not erupt until 14½ months of age.

After 5 months of thyroid therapy the umbilical hernia had vanished and only a tiny opening could be felt (fig. 4).

At the end of 7 months' treatment when the child was 16 months old her mental status was considered to have reached an age of 9 months. When 17 months old the bone age was estimated at 1 year.

Case 2, J. S. (University of California Hospital, O. P. D., No. *U* 61107). This boy was normally delivered at term, weighing 9 lb. Jaundice, or possibly carotinemia, lasted until the age of 2 months. There was no history or evidence of thyroid or iodine disturbance in the mother. The pregnancy and birth took place in an area where goiter is not endemic and the child was reared there. However, the maternal aunt and grandmother had had difficulties with goiter.

When the boy was 2½ months old the parents sought medical aid chiefly because nursing had frequently induced strangulation since birth. Also he had a deep cry. He had gained only one pound in 2½ months. He was constipated. His hands and feet were always cold, pale and mottled. An umbilical hernia, the size of a walnut, was enlarging steadily. He slept inordinately long—17 hours daily. However, when 6 weeks old he began to raise his head and since 8 weeks of age he has raised his trunk and turned over.

Received for publication March 8, 1941.

The patient was 21½ in. long, which was short for his age. His face, with its puffy bloated features resembled a frog's. The voice was deep and bass-like; the mouth large; the tongue wide and thick; his hair was coarse and sparse; the skin was of good color but dry, coarse and scaly, especially on the arms and legs. The anterior fontanelle showed no tendency to close. The abdomen protruded due to gaseous distension from poor muscle tone; an umbilical hernia was very large and shaped like a mushroom. A small thyroid gland was palpable. Mental activity was definitely retarded.

The blood cholesterol was normal (183 mg.%). A barium visualization suggested a retropharyngeal mass. The epiphyseal development was retarded; the proximal epiphysis of the tibia and the cuboid which are normally present at birth, were absent.

During the first month's treatment (first started at the age of 2½ months with a daily dose of 0.3 to 0.5 grains of thyroid substance) the following improvement occurred: the strangling attacks disappeared rapidly; the constipation diminished; there was a gain of 3½ in. in height and 2 lb. in weight. The hernia was visible only when the infant cried but the opening was still easily palpable. Nevertheless the shrinkage of the hernial sac and the diminished aperture were very impressive.

Thyroid therapy was discontinued for the next 6 weeks and at the end of this period tests by the ingestion of radioactive iodine disclosed that the baby's thyroid gland

Fig. 1–4. *Case 1, M. M.* Fig. 1. BEFORE THERAPY. Fig. 2. THE UMBILICAL HERNIA BEFORE TREATMENT was about the size of a large walnut and the opening admitted the end of a small finger. Fig. 3. AFTER 6 WEEKS' TREATMENT with 0.3 grain of thyroid extract daily. Notice the great transformation of the features. Fig. 4. AFTER 5 MONTHS' TREATMENT, showing the absence of hernia; only a tiny opening could be felt. (After 6 weeks' treatment the umbilical hernia had practically disappeared. The daily dose of thyroid extract was increased to 0.75 grain after the 6th week.)

assimilated only very small traces. All of the previous reported abnormalities recurred. The hernia became as large and as conspicuous as it was originally. The blood cholesterol had risen to 253 mg.%.

Therapy was reinstituted at 5 months of age and shortly thereafter all of the previous beneficial transformations were reduplicated.

opening was closing steadily. No truss was used at any time.

After 7 months of treatment the daily dose was raised to 0.5 grains of thyroid substance daily. After 8 months of treatment the umbilical hernia could scarcely be detected by palpation even though the abdomen was distended. The epigastric hernia was barely noticeable (fig. 6).

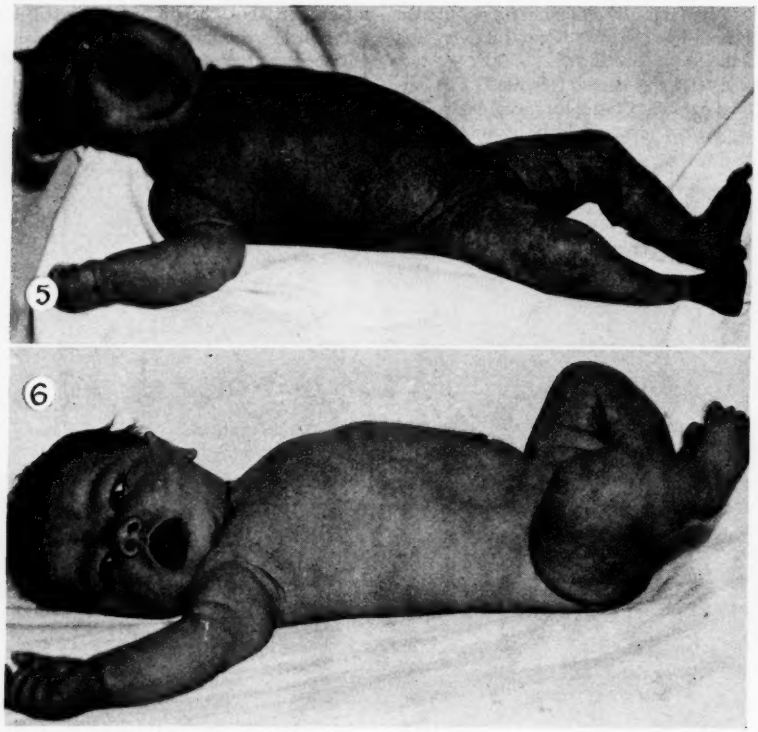

Fig. 5. *Case 3, D. B.* BEFORE TREATMENT. The umbilical hernia was large and an epigastric hernia was present. Fig. 6. AFTER 5 MONTHS OF THERAPY. The opening was barely palpable.

Case 3, D. B. (University of California Hospital, O. P. D., No. *U 39601*). This baby girl was obviously hypothyroid at birth. She was pale; the eyelids were myxedematous as were other puffy areas, particularly the face, the large tongue, larynx, backs of hands, lumbar area, lower legs and the dorsum of the feet. Constipation was very bothersome, causing gas pains and tenesmus during evacuation. A large hernia of the umbilicus and a smaller epigastric one were noted soon after delivery (fig. 5).

At 2¾ months of age thyroid therapy was begun. The dose was 0.1 grain of powder in 2 oz. of milk formula, twice daily. In the amazingly brief time of 10 days the constipation was notably diminished. This treatment was stopped for 10 days and the constipation recurred as severely as before. From the age of 3¼ months treatment was administered faithfully, the dosage being 0.3 grain daily.

After 3 months of treatment the hernial protrusion was only occasionally visible, especially during crying. The

The experience as noted in these three cases has been observed in a fourth case now under treatment. It is interesting that in congenital hypothyroidism umbilical hernias occur far more frequently than inguinal rupture. In normal newborns tiny umbilical hernias are not uncommon but disappear ordinarily as the infant develops stronger abdominal muscles.

In two of the four infants studied a very definite diastasis recti was noticeable and likewise vanished under treatment. The deficient tonus in bowel and abdominal wall muscles plus abnormally slow peristalsis, both due to lack of thyroid hormone, no doubt account for hernial tendency. These factors favor gaseous distension and hence further aggravate the protusion. There may be an additional factor in the nature of a congenital defect in the size of the umbilical opening. The actual size of the opening itself

is probably of greater therapeutic significance than the sac and contents on the outside. If the aperture is not large enough a distended bowel may readily strangulate after incarceration; surgery then becomes an immediate necessity. Yet, if the orifice is exceptionally large thyroid medication alone may not be effectual.

In the cases herein reported, the largest hernial opening was only 1 cm. in diameter, which size is amenable to thyroid medication. If the opening were 2.5 cm. or more in width hormone therapy probably would not have sufficed. It will be noted that no supportive truss was used. This was not considered necessary. Surgical intervention never became an emergency or necessity.

It will be noted that in the first case, the hernial sac had practically disappeared and the orifice had become much smaller after only 6 weeks. In the second case, after only 10 days of medication, constipation had been alleviated; after 3 months the hernia had become much smaller and only appeared after vigorous crying. In the third patient, the constipation disappeared after one month, and the opening was very much smaller, the hernia only appeared after severe crying and had shrunk from the size of a mushroom to that of a pea. After 5 to 7 months therapy in all cases the openings were no longer palpable and no herniae were visible after the most vigorous strains.

Such response is deemed very satisfactory. Truss protection will not produce as good results. Operative repair is more certain and immediate, but rarely necessary. Such herniae may recur later in life; if so surgery is indicated, but in infancy thyroid medication should be given adequate trial.

GROWTH MEASUREMENT

A STATUROGRAM BASED ON AGE-MEASUREMENT RELATIONSHIP

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AGE-MEASUREMENT RELATIONSHIP is usually based on a numerical comparison of the actual with the fixed average normal dimensions for a given age. Another method for establishing age-measurement relationship depends upon making a comparison between actual data and values occurring within a minimum and maximum range for a given age. The foregoing numerical data are frequently supplemented, also, by periodic pictorial miscellany which more often than not has a greater scrap-book than scientific value.

The chart submitted with this description was prepared from Engelbach's[1] data on measurements in relation to age and a modification of a record form used in the Department of Physical Education of the University of Kansas by the late Dr. James Naismith. Engelbach's table provides the minimum and maximum values for males and females from one month to twenty years of age. From these statistics were calculated average age-measurements of both sexes for 7 to 20 years.

The essential statural dimensions given for the male from 7 to 20 years of age, inclusive, are: (1) height, (2) weight, (3) span, (4) circumference of head, chest and waist, and (5) length of upper and lower segments. These essential dimensions are listed for the female, also, except that specifications of the above-captioned circumferences (head, chest and waist) are deleted after the seventeenth year.

The numerical data are listed in perpendicular columns each headed by the age in years. Each division of the columns formed by ordinates and abscissae is divided diagonally in order that the average values for both sexes can be recorded within the same column for the respective age period.

It is obvious that the use of average age-measurements connote "ideal" rather than normal values. Actual measurements of either sex, therefore, in agreement with all the figures in any age column would plot a perpendicular line. Doubtless subjects conforming to the ideal dimensions might be encountered rarely. In the practical application of this chart, however, it is more likely that the shift of the graph to either side of the ideal perpendicular will be more frequent than the contrary.

An actual age-measurement record is illustrated in figure 1. The subject of this survey was a negro male, 13 years of age. When a numerical comparison is made of his actual and ideal values, the statural asymmetry, while apparent, is far from striking. Graphically portrayed by superimposing on the table straight lines connecting the actual numerical values, his abnormal statural configuration immediately arrests attention. This form of "staturogram" not only delineates bodily development but provides all the pertinent dimensions for a permanent record.

In the event that several staturograms are to be recorded during a year, instead of using a separate chart on each occasion, the abscissa at the head of the proper age column can be divided into quarters and the graph started from the quarter nearest the exact age. Confusion due to intersecting lines of two or more graphs can be avoided by differentiating with colors or using various well known types of broken lines.

There is one blank column on each side of the chart. These are for the purpose of inserting actual measurements for which there are no correlative averages. For example: A height in excess of 64 inches is not infrequent in the eunuchoid female, or the weight in Fröhlich's syndrome usually is far in excess of the fixed normals in this chart. Such phenomenal values can be inserted in the right hand column and

Received for publication December 19, 1940.

[1] ENGLEBACH, W.: *Endocrinology* 16:6. 1932.

abnormally low dimensions can be recorded in the left hand column.

SUMMARY

There is described and illustrated a new table for the determination and recording of statural measurements in relation to age. The essential dimensions for males and females from seven to twenty years of age, inclusive, are covered in the table. The values are averages derived from Engelbach's table of measurements. A graphic representation of statural development (staturogram) can be superimposed on the table as a permanent record.

AGE - MEASUREMENT STATUROGRAM

Name Charles Hagans Age 13 Sex ♂ Race Col No. Special

Address 3026 Stanley City Detroit State Michigan

Diagnosis Sickle Cell Trait Date April 30 1940

Age (Years)	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Height (Inches)	46.8 / 47.2	48.9 / 49.2	50.9 / 51.2	53.0 / 53.2	55.3 / 55.2	57.5 / 57.1	59.7 / 58.9	61.4 / 60.7	62.5 / 62.4	63.2 / 64.0	63.7 / 65.4	64.0 / 66.6	67.5	68.0
Weight (Pounds)	47.2 / 48.1	52.0 / 54.8	57.4 / 58.0	63.6 / 64.3	72.4 / 71.2	80.6 / 78.3	90.0 / 85.8	101.4 / 92.0	107.7 / 101.4	110.9 / 109.0	114.2 / 117.7	117.5 / 124.4	131.4	135.0
Span (Inches)	46.0 / 46.1	48.2 / 48.6	50.4 / 51.0	52.6 / 53.4	55.3 / 55.6	57.9 / 57.9	59.7 / 60.4	61.3 / 61.9	63.0 / 64.1	63.6 / 65.8	64.2 / 67.5	64.8 / 68.6	69.8	70.4
Head (Inches)	20.3 / 20.6	20.4 / 20.7	20.5 / 20.9	20.7 / 21.0	20.9 / 21.1	21.0 / 21.2	21.2 / 21.4	21.4 / 21.6	21.6 / 21.8	21.7 / 22.0	21.8 / 22.2	22.4	22.5	22.5
Chest (Inches)	22.7 / 23.3	23.4 / 24.0	24.2 / 24.6	25.0 / 25.2	26.1 / 26.1	27.1 / 27.0	28.1 / 28.0	28.9 / 29.1	29.6 / 30.3	30.1 / 31.7	30.5 / 32.9	33.7	34.4	34.7
Waist (Inches)	20.5 / 21.3	20.8 / 21.8	21.2 / 22.3	21.8 / 22.8	22.4 / 23.3	23.2 / 23.9	23.9 / 24.6	24.5 / 25.4	24.8 / 26.4	25.1 / 27.2	25.3 / 27.8	28.2	28.5	28.7
Upper (Inches)	24.4 / 24.6	25.1 / 25.1	25.8 / 25.9	26.7 / 26.7	27.8 / 27.4	28.7 / 28.3	29.6 / 29.1	30.6 / 29.8	31.2 / 30.8	31.5 / 31.5	31.8 / 32.2	32.1 / 32.8	32.1 / 33.4	32.1 / 33.7
Lower (Inches)	22.6 / 22.4	23.9 / 23.8	25.1 / 25.1	27.1 / 26.3	27.1 / 27.6	28.8 / 28.7	29.9 / 29.9	30.9 / 30.7	31.3 / 31.2	31.5 / 32.5	31.7 / 33.3	31.9 / 33.7	31.9 / 34.1	31.9 / 34.3

N.B. Measurements for females are in upper and males in lower division.

Remarks: R.B.C. 50. Hb. 85%. Retic. 3.1% M.D. 7262. W.B.C. 11,200
10% sickle cells in 4 hours

E Fisher

M.D.

DIABETES MELLITUS

USE OF ANTERIOR PITUITARY EXTRACTS IN UNCONTROLLED DIABETES MELLITUS WITH GROWTH AND SEXUAL RETARDATION

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THE WORK of Houssay (1) and subsequent investigators has caused much discussion regarding the etiologic role played by the anterior lobe of the pituitary gland in diabetes mellitus in man. The injection of extracts of the anterior lobe of the hypophysis has produced diabetes in dogs (2) and has made the diabetes more severe in the cases reported by Lassen and Hansen (3). It has been postulated that the hypophysis secretes an excessive amount of the diabetogenic factor in cases of diabetes mellitus in man.

It is for this reason that we are reporting three cases of diabetes mellitus in which we employed extracts of the anterior lobe of the pituitary gland[1] containing the alleged growth hormone. The diabetes was improved in one case and was unaltered in the other two.

Case 1. A white boy, aged 15 years, entered the University Hospital in November, 1928, because of diabetes mellitus of 2½ years' duration. His size and development were approximately normal for a boy of this age. There were no remarkable abnormalities. The height was 61¼ in., and the weight was 91 lb. The diabetes was difficult to control; he remained in the hospital 86 days, during which time he gained 15 lb. in weight. He was sent home with instructions to take 51 U of insulin daily, and with a diet which contained 55 gm. of protein, 55 gm. of carbohydrate, and 150 gm. of fat. He returned to the hospital in May, 1929, because of increasing glycosuria. The diabetes had not been controlled and he had lost 9 lb. in weight. After 33 days the diabetes was under control, and he was sent home with instructions to take 38 U of insulin daily. Shortly thereafter it became necessary for him to support himself. He began to eat what foods he could afford, but took sufficient insulin to prevent acidosis. At none of the infrequent times that the urine was examined was it free of sugar. On this regimen he worked most of the time for 9¾ years without any illness, but he failed to grow or develop. In February, 1939, he returned to the hospital at the age of 25 years. He appeared to be approximately 15 years of age. There was no beard, the axillary and public hair was thin, the genitalia were small, and the voice was high pitched. His height was 62¾ in., and his weight 104 lb. The urine contained a large amount of dextrose, but no acetone bodies. Roentgenograms showed epiphyses corresponding to the age of about 16 years. We were unable to control the diabetes during the first month with a diet containing 70 gm. of protein, 126 gm. of carbohydrate, and 120 gm. of fat, and by the administration of various doses of insulin, distributed over a variety of periods during the day and night. Insulin was then administered in doses of 8 U every 3 hours, day and night, for 17 days. During this time the dextrose content of the urine fluctuated between 40 and 130 gm. daily. Without alteration of the diet or insulin dosage, an extract of the anterior lobe of the pituitary gland was administered in doses of 30 R.U. every other day for two months. The dextrose excretion declined to from 0 to 20 gm. daily. After the amount of insulin had been changed to 75 U, divided into 4 daily doses, the dextrose content of the urine varied from 0 to 10 gm. This excretion of dextrose continued after the insulin administration was changed to 60 U of protamine zinc and 15 U of regular insulin daily. The anterior pituitary extract was then administered in doses of 30 R.U. twice weekly for another two months. The urine became free of sugar and the insulin was reduced to 40 U of protamine zinc insulin daily. During the 4 months of treatment with the pituitary extract the patient grew 1¼ in. in height and gained 36 lb. in weight; his voice changed, and he appeared older. He was sent home with instructions to

Received for publication January 21, 1941.

[1] The anterior pituitary extract used was supplied as Antuitrin-G by Parke, Davis & Co., Detroit, Michigan.

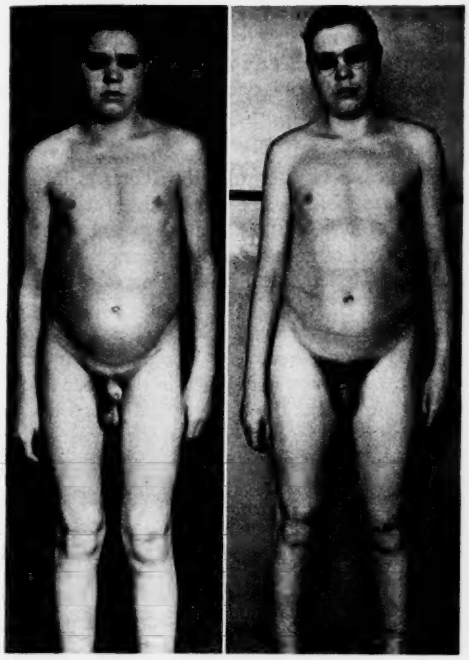

Fig. 1. THE SEXUAL DEVELOPMENT IN *case 1* BEFORE AND ONE YEAR FOLLOWING INSTITUTION OF TREATMENT

continue the above diet, and to take 40 U of protamine zinc insulin daily, and 30 R.U. of the extract of the anterior lobe of the pituitary gland twice a week. After 3 weeks at home he was unable to obtain the pituitary extract, but gradually reduced the insulin to 30 U daily; except for an occasional insulin reaction the diabetes remained well controlled. He returned to the hospital in April, 1940, and with reduced activity, 50 U of protamine zinc insulin were required to control the diabetes. His height was 64 in., his weight 137 lb., and roentgenograms showed epiphyses corresponding to an age of 17 years. The extract of the anterior lobe of the pituitary gland was again administered in the same dose as before, and, 113 days later, he had grown ½ in. and the insulin requirement had declined to 35 U daily. The changes in sexual development are shown in figure 1.

Case 2. A white boy, aged 11 years, entered the University Hospital in January, 1933, because of diabetes mellitus of 8 years' duration. The diabetes was controlled fairly well for the first two or three years, but not thereafter. His growth practically ceased after the onset of the the diabetes. He was underdeveloped and malnourished, and appeared to be 5 or 6 years of age. His height was 44½ in. and his weight 38¾ lb. For the next 6½ years his treatment was supervised by members of the Pediatric Department; the diabetes was difficult to control during this period. He grew to 61¼ in. in height, and his weight increased to 101½ lb., but the secondary sexual characteristics failed to develop. He appeared to be 13 or 14 years of age, with a high-pitched voice. There was no beard, the axillary and pubic hair was thin, and the genitalia were small. He required 65 U of insulin daily, with a diet which contained 320 gm. of what was potentially dextrose. An extract of the anterior lobe of the pituitary gland was administered parenterally in doses of 30 R.U. every other day for 35 days, and then 30 R.U. twice a week about one-half of the time for the next 3 months. The voice changed, the genitalia enlarged, and he grew 1½ in. in height, but the diabetes did not improve.

Case 3. A white girl, aged 9 years, entered the University Hospital in October, 1931, because of diabetes mellitus of 10 months' duration. She had always been small and growth ceased after the onset of the diabetes, which had not been controlled. She was underdeveloped and malnourished, and appeared to be 5 years of age. Her height was 44½ in., and her weight was 37¼ lb. For the next 8 years her treatment was supervised my members of the Pediatric Department; the diabetes was difficult to control during this period. She grew in height to 53½ in., and her weight increased to 83¼ lb. At this time, when she appeared to be 12 years of age, the additional diagnosis of pituitary dwarfism was made. The breasts were underdeveloped, and she had not menstruated. Roentgenograms showed that the bone development was what would be expected for a person of 12 years. She required 14 U of insulin daily, with a diet containing 219 gm. of what was potentially dextrose. An extract of the anterior lobe of the pituitary gland was administered parenterally in doses of 30 R.U. every other day, for 35 days, and then 10 R.U. twice weekly, together with desiccated thyroid gland 1 grain orally, each day, for 6½ months. She grew 1 in. in height with the epiphyses changing to that corresponding to 14 years but her diabetes was not altered.

DISCUSSION

We hesitated to administer extracts of the anterior lobe of the pituitary gland to patients with diabetes mellitus because the experimental work on dogs and that of Lassen and Hansen on patients indicated that the diabetes would probably become more severe. On the other hand, the diabetes was apparently not altered in Beck and Suter's (4) case. Our first patient appeared to be suitable for such therapy. He was 25 years of age, with open epiphyses and sexual immaturity. This underdevelopment we attributed to the fact that the diabetes had not been controlled, but we were unable to control it adequately. It appeared, therefore, that additional therapy was indicated.

The fact that his diabetes improved after anterior pituitary extract therapy, without alteration of diet or insulin dosage, and with no evidence of infection, indicates that the diabetes improved because of the additional therapy. The explanation for the improvement, however, is not clear. It may be that the increased growth rate and the production of puberty were important factors in such improvement. On the other hand, the diabetes was not improved in the other two cases. It is possible that the first case was

one of primary pituitary dwarfism, but we do not think so. It is difficult to attribute the improvement of the diabetes to partial or complete eradication of pituitary deficiency. In addition, there is the added difficulty that the diabetes was not altered in *case* 3, which was one of primary pituitary dwarfism.

There is no doubt that it would be deleterious to administer to a patient with diabetes mellitus an extract of the anterior lobe of the pituitary gland which contained a large amount of the diabetogenic factor. It appears, therefore, that the extract administered by us contained very little or none of this factor, or if so, that it was present in amounts insufficient to counteract the beneficial effect.

Our observations lead us to believe that the administration of extracts of the anterior lobe of the pituitary gland which contain the alleged growth hormone may be of value in the production of growth and sexual development in certain cases of diabetes mellitus in which these are retarded, and in a rare instance may aid in controlling the previously uncontrollable diabetes. It is not our opinion that such extracts should be administered in every case, but we think that, at first, every effort should be made to control the diabetes adequately. Most patients will grow and develop sexually after the diabetes is controlled. In the rare case in which the diabetes cannot be controlled sufficiently well to permit normal development, the pituitary extract therapy should be considered.

SUMMARY

Three cases of uncontrolled diabetes mellitus are reported, in which we observed the effects upon the retarded growth and sexual development, and upon the diabetes, of extracts of the anterior lobe of the pituitary gland containing the alleged growth hormone.

The growth rate and sexual development were accelerated in the three cases. The diabetes improved in one case and was not altered in the other two.

It is emphasized that growth and sexual development will occur in most cases after the diabetes has been controlled adequately, and that pituitary extract therapy is indicated in the exceptional case only.

REFERENCES

1. Houssay, B. A., and A. Biasotti: *Endocrinology* 15: 511. 1931.
2. Young, F. G.: *Biochem. J.* 32: 513, 524. 1938.
3. Lassen, H. C. A., and L. Hansen: *Act. Med. Scand. Supp.*, 89, 288. 1938.
4. Beck, H. G., and G. M. Suter: *Endocrinology* 22: 115. 1938.

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: HANS O. HATERIUS. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, ARTHUR GROLLMAN, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. C. PFEIFFER, GEORGE W. THORN, EMMERICH VON HAAM.

HYPOPHYSIS

BAIOCCHI, P.

Prepituitary therapy in a fracture with persistent delay of osseous consolidation. *Riv. chir.* 5: 423. 1939. *Rev. sud-am. de endocrinol.* 23: 649. 1940.

A case of fracture of the arm that showed no signs of consolidation after 9 months being treated with vitamin D, Ca intravenously and breaking up of the callus, without success, responded promptly to intrafocal administration of anterior pituitary extract.—A. E. M.

BOEDEKER, R. V.

A clinical study of the increased response of the full-term gravid uterus to pituitrin after alkalinization. *Am. J. Obst. & Gynec.* 41: 84. 1941.

A study was made as to the effect of 'alkalinization' and 'acidification' upon the sensitivity of the gravid uterus at term to the fractional administration of pituitrin (2 minim doses, every 20 minutes for 8 doses or until onset of labor). Ninety-four medical inductions of labor were attempted after 'alkalinization' of the patients by 40 gm. of sodium bicarbonate or 60 gm. 'citrocarbonate' (Upjohn) given in divided doses, beginning a day prior to the administration of pituitrin. Twenty medical inductions were attempted after 'acidification' of the patients with ammonium chloride 4 to 6 gm. daily for 3 days prior to pituitrin administration. One hundred and thirteen inductions were attempted without any preliminary 'alkalinization' or 'acidification.' Labor was induced in 70% of the 'alkalized' patients, in 40.7% of patients not given either 'alkalinizing' or 'acidifying' therapy and in only 15% of the 'acidified' patients.—*E.C.H.*

GREENE, J. A., AND L. E. JANUARY.

Diabetes insipidus treated by the subcutaneous administration of a suspension of pitressin tannate in oil. *J.A.M.A.* 115: 1183. 1940.

The authors studied the effect of the administration of pitression tannate in oil to 3 patients with diabetes insipidus and to 3 cats with experimentally produced diabetes insipidus. The administration of 5 pressor units of pitressin tannate in oil resulted in a prolonged therapeutic effect, varying from 30 to 82 hr. in the patients and from 3 to 7 days in the cats. There were no disagreeable side effects.—D. J. Stephens.

HUTCHISON, H. E.

Necrosis of the anterior lobe of the pituitary during pregnancy. *J. Path. & Bact.* 51: 442. 1940.

A case of massive necrosis of the anterior lobe of the pituitary in a pregnant woman is reported. It is thought that this had resulted from circulatory collapse produced by pulmonary embolism and the relation of the lesion to a coincident necrosis of the corpus luteum is discussed.—*H. E. Hutchison.*

MOGENSEN, E.

Three cases of Simmonds' syndrome. With special reference to clinical diagnosis and hormone treatment. *Acta med. Scandinav.* 105: 378. 1940.

Two ♂ cases were markedly improved after treatment with chorionic gonadotropin and one ♀ showed improvement with estrogen. The three cases are described in detail, but the diagnosis of Simmonds' syndrome is not based on postmortem examination.—*E.B.A.*

MOGENSEN, E.

Simmonds' syndrome. A review. *Acta med. Scandinav.* 105: 360. 1940.

A consideration of 94 references has led the author to a redefinition of this disease. An account of the etiology, symptoms, diagnosis, and treatment is given.—*E.B.A.*

SUTTON, D. C.

Inter-relation between the vitamin B complex and the anterior lobe of the pituitary gland. *South. M. J.* 34: 47. 1941.

The records of 3 cases are given. From these the authors conclude in part "That an extract of the anterior lobe will cause recovery of pellagra lesions when they have failed to respond to nicotinic acid, riboflavin, parenteral liver and adequate diet." It is suggested that the anterior lobe hormones are essential to the utilization of the vitamin B complex.—*J.C.D.*

PANCREAS

BAYER, L. M., AND J. H. DAVIS.

Nondiabetic glycosuria in children. Report of nine cases. *Am. J. Dis. Child.* 60: 580. 1940.

A series of cases is presented which gives support to an optimistic outlook with regard to prognosis of children with atypical glycosuria. The glycosuria was either called nondiabetic or diabetic with definite reservations at the

time of the first visit. These children were followed for periods of from 2 to 11 years with either moderate or no restriction of carbohydrates. At the time of report not a single one of them was diabetic.—*M.B.G.*

BOGAN, I. K.

Hands and wrists of the diabetic child. A roentgenologic study. *Am. J. Dis. Child.* 59: 850. 1940.

Roentgenograms of the hands and wrists of 95 boys and of 74 girls were studied on the basis of Todd's and Flory's standards of bone development. The bone age is equal to the chronological age in 25.9% of the boys and in 33.2% of the girls, is retarded in 60.2% of the boys and in 51.1% of the girls and is accelerated in 13.8% of boys and in 15.6% of girls. The retardation of bone age was more than 2 years in 20.7% of the children and more than 3 years in 13.6%. The retardation was greater in boys than in girls. The longer the duration of the disease the greater was the tendency to retardation. Anomalies and developmental defects were observed in one-fourth of these diabetic children.—*M.B.G.*

CHIOVENDA, M.

The endocrine portion of the pancreas in cachexia from malignant tumors, tuberculosis and other diseases, on the basis of islet volume, islet and islet cell number and histology. *Ormoni, Turin* 2: 3. 1940.

Through study of sections of pancreas, total volume and total number of islands were estimated. Total insular cells were also determined. Fifty-one glands were examined. Of these 15 had cachexias due to malignant tumors, 1 tumor without cachexia, 12 cachexias from other causes, 10 chronic tuberculosis with cachexia, 3 lymphogranulomas, and 10 acute non-cachectic diseases. The latter group was taken as a control. All cachexias except that of tuberculosis caused an increase in number and volume of islands, particularly in younger patients. In chronic tuberculosis, the volume and number of island cells decreased, but not the number of islands. Since the cachexias, except that of tuberculosis, showed a decrease in total pancreatic volume, these results indicated a true hyperfunction of insular tissue. This is believed to occur as a parasympathetic-hypoglycemic response to antagonize adrenal and thyroid hyperfunction.—G. A. E.

COMFORT, M. W.

Tests of pancreatic function. *J.A.M.A.* 115: 2044. 1940.

Comfort advises the use of a double-barreled duodenal tube for collecting the external pancreatic secretion. Purified secretin is given intravenously, or mecholyl HCl is given subcutaneously in a dose of 15 mg. Samples are collected every 10 minutes, and volume, PH, amylase, and total excretion of bicarbonate are determined. These tests combined with serum and urinary lipase and amylase, and glucose tolerance tests supply information aiding in the diagnosis of chronic sclerosing pancreatis and malignancy of the pancreas.—C. P.

GRAHAM, G.

A review of the causes of diabetes mellitus. *Brit. M. J.* 1940. p. 479.

The following topics are discussed: changes in the β cells; the pituitary gland and sensitivity to insulin, showing the very close relation between the anterior pituitary and the islands of Langerhans. In the absence of the pituitary less insulin is needed; substances inhibiting insulin action; types of diabetic patients; insulin dosage; variations in response to insulin; 41 references.—J. B. Paton.

GREENE, J. A., L. W. SWANSON AND C. A. JACOBS.

Control of diabetes mellitus. *J.A.M.A.* 115: 1518. 1940.

Greene and his colleagues studied a group of 324 diabetic patients in regard to blood sugar levels and the healing of clean operative wounds. They also studied wound healing in a group of 35 patients in whom an unusually high blood sugar level was maintained. They divided their cases into 2 groups depending on whether the operation had been in an area of good or poor blood supply. They conclude that elevated blood sugar levels and glycosuria do not contribute to delayed healing of wounds, nor do these factors increase the incidence of infection of clean wounds. They ascribe the 4% increase in delayed healing of wounds which they found in diabetics to arteriosclerosis and poorer utilization of dextrose.—C. P.

JOSLIN, E. P.

The universality of diabetes, a survey of diabetic morbidity in Arizona. *J.A.M.A.* 115: 2033. 1940.

Joslin has shown by comparing the diabetic statistics of the state of Arizona with those of the National Health Survey that the incidence of diabetes is greatest where: (1) the average age is the greatest; (2) women predominate; (3) obesity is most frequent; (4) the proportion of Jews is greatest; (5) medical supervision is closest; (6) deaths are most accurately reported.—C. P.

MARGOLIS, H. M., AND V. W. EISENSTEIN.

The treatment of diabetes mellitus with a four-meal diet: A means of circumventing certain difficulties arising in the use of protamine zinc insulin. *Ann. Int. Med.* 14: 667. 1940.

The four-meal regimen affords the utmost simplicity of diabetic treatment. A single daily injection of protamine Zn insulin suffices for control. Neither supplementary doses of soluble insulin nor feedings between meals are necessary with this regimen. Smoother, quicker, more adequate control of diabetes is made possible, even in severe cases, with minimal doses of protamine Zn insulin. The grave danger of hypoglycemic shock, and hence the possibility of insulin fatalities, are eliminated by the use of a "protective 4th meal." The satiety, contentment, and morale of diabetic patients are enhanced by the use of 4 meals daily. The 4-meal regimen makes the treatment of diabetes mellitus with protamine Zn insulin a safe and practical procedure for office and clinic use.—*Authors' summary.*

MILLER, H. C., AND R. A. ROSS.

Relation of hypoglycemia to the symptoms observed in infants of diabetic mothers. *J. Pediat.* 16: 472. 1940.

Hypoglycemia may be found without symptoms in new born infants of non-diabetic mothers and also of

diabetic mothers. Cyanosis, muscular twitchings and convulsions in a new born infant of a diabetic mother are not always due to an associated hypoglycemia. The authors report 6 new born infants with hypoglycemia, 3 of whom were symptomless, 2 had acute congestive cardiac failure and one had a probable erythroblastosis fetalis and cerebral hemorrhage. Parenteral administration of glucose was of no benefit in any one of the cases. The authors suggest that the symptoms were due to an organic disease and not to the hypoglycemia.—M. B. G.

Root, H. F.

Diabetic control versus caloric sufficiency in the treatment of diabetes and pulmonary tuberculosis. *Am. J. M. Sc.* 200: 53. 1940.

In a review of the possible etiologic factors in 396 cases of pulmonary tuberculosis in diabetic patients, limitation in calories appeared to have less influence than lack of control of the diabetes. Acidosis or coma preceded the development of tuberculosis in at least 20% and probably nearly 50% of the cases. The use of insulin and diets adequate not only in the balance of carbohydrate, protein and fat, but in their content of vitamins and minerals is emphasized. The tuberculosis death rate among diabetics per 1000 fell from 11 prior to the use of insulin to 4.1 during the first 6 years after the use of insulin.—Author's summary.

Shirley, H. F., and I. M. Greer.

Environmental and personality problems in the treatment of diabetic children. *J. Pediat.* 16: 775. 1940.

Successful treatment of diabetes in children depends upon a long-range, well-planned program which includes careful evaluation and treatment of economic, social, home, personality and behavior problems. Attention must be paid also to thorough instruction of the parents in the management of the child, maintenance of the closest cooperation of parents and child, prevention and correction of faulty parental attitudes and finally, constant encouragement of the child to live a normal happy and useful life.—M. B. G.

Sisson, W. R.

The neonatal problem in infants of diabetic mothers. *J.A.M.A.* 115: 2040. 1940.

In a study of 65 infants of diabetic mothers Sisson has not found a definite neonatal syndrome of hypoglycemia, but has found a syndrome characterized by a high incidence of primary atelectasis and cerebral anoxia. The mortality rate was 18%. Oxygen therapy was found to be the best treatment, while parenteral dextrose after birth was not found to be of value.—C. P.

White, Priscilla and Hazel Hunt.

Prediction and prevention of pregnancy accidents in diabetes. *J.A.M.A.* 115: 2039. 1940.

The authors believe that an abnormal rise of chorionic gonadotropin in diabetics after the 20th week to a level of 200 R.U./100 cc. is accompanied by premature delivery, stillbirth, and neonatal deaths. These accidents are caused by a failure of production of, or a failure in metabolism of estrogen and progesterone. In a series of 61 cases complications have been prevented by continuous therapy with estradiol, benzoate proluton, stilbestrol, and pregnolinine. The fetal survival was 92% when hormonal balance was normal, 42% with abnormal hormonal balance, and 87% where the hormonal balance was adequately corrected.—C. P.

PARATHYROID

Bakwin, H.

Tetany in newborn infants. Relation to physiological hypoparathyroidism. *J. Pediat.* 14: 1. 1939.

Tetany in the newborn may be either physiological or pathological, and is associated with hypoparathyroidism. Physiological hypoparathyroidism results from a low content of parathyroid hormone and calcium in the new born. Pathological hypoparathyroidism results from either increase in phosphates endogenously released during physiological starvation of the new born or ingested from without by cow's milk which contains large amounts of phosphates.—M. B. G.

Bloxsom, A.

Treatment of tetany of the new born infant with dihydrotachysterol. *J. Pediat.* 16: 344. 1940.

Dihydrotachysterol was administered to a 3-week-old infant who was believed to have parathyroid tetany on the basis of chemical findings (serum calcium 5.4 mg. per 100 cc. and phosphorus, 6.2 mg.) and clinical symptoms (twitchings, positive Chvostek's sign, cyanosis). Large doses of the drug were necessary to relieve the condition; it was started at five drops a day and gradually increased up to 15 drops 3 times daily.—M. B. G.

Chu, G. T., and C. Sung.

Tetany in infancy and childhood. *J. Pediat.* 16: 607. 1940.

This report is based upon a study of 45 cases of tetany in Peiping, China. The material differs from that in the Western literature in that many of the cases (66%) occurred in infants below 3 months of age; the marked incidence of impaired calcium metabolism in the mothers during pregnancy and lactation (80%); and the frequent occurrence of rickets during the first 3 months of life (72%). Convulsions were the most frequent symptoms in the infants while carpopedal spasm and laryngospasm were relatively infrequent. The authors state that in a community where the mother's nutrition is deficient in calcium or vitamin D, maternal milk is not to be relied upon as an anti-tetanic agent.—M. B. G.

Crawford, T.

Carbohydrate tolerance in hypothyroidism and hyperthyroidism. *Arch. Dis. Child.* 15: 184. 1940.

Oral glucose tolerance tests in 6 cretin children showed increased tolerance in 4, decreased or normal in 2. Intravenous tests in every case showed decreased tolerance. Upon treatment the curves tended to approach normal unless an artificial hyperthyroidism was caused. Then, and in 2 cases of hyperthyroidism, oral tests showed normal or decreased tolerance, intravenous tests decreased tolerance. The low oral curve and fasting blood glucose

levels ('increased tolerance') in hypothyroidism are considered due to the faulty absorption known to occur in myxedema; the decreased tolerance of intravenous tests, to a slowing of the rates both of glucose oxidation and its storage as glycogen. The decreased intravenous tolerance of hyperthyroidism is explained by the failure of normal glucose storage as glycogen to the extent of overshadowing any increase in the rate of glucose oxidation. It is suggested that the correct level of thyroid treatment might be recognized as the highest compatible with a normal intravenous curve.—Kathryn Knowlton (*Chemical Abstracts*).

GARRAHAN, J. P., AND G. F. THOMAS.

Calcium fractions in infantile spasmophilia. *Am. J. Dis. Child.* 60: 249. 1940.

Observations on 6 cases of infantile spasmophilia led the authors to believe that in this condition the diffusible Ca remains at normal levels, sometimes above normal, while the non-diffusible Ca is greatly reduced (between 2.2 and 0.7). As the condition progresses toward healing, the non-diffusible fraction increases and the diffusible Ca remains the same or shows slight increases. The Ca in the spinal fluid, which the authors regard as diffusible Ca, is not affected in spasmophilia.—*M.B.G.*

NELSON, C. F., AND R. C. NELSON.

The medical management of fractures. *J.A.M.A.* 116: 184. 1941.

Parathyroid extract is given along with calcium gluconate and vitamin D to promote the healing of fractures. One cc. of parathyroid extract mobilizes calcium from the trabeculae, and this is followed by marked osteoblastic activity. One cc. is given every 3 days for 3 to 5 doses. Then one cc. every 7 days for 5 or more doses is recommended. The serum calcium should be maintained at 10.5 to 12.0 mg.%. Hypocalcemia may result from either hyper- or hypothyroid function.—C. P.

ROSENBERG, E. F.

Chalk gout. *J.A.M.A.* 115: 1791. 1940.

Rosenberg reports on two cases of 'chalk gout' calcinosis circumscripta, and summarizes the existing knowledge of this rare disease with regard to etiology, clinical and pathological findings, and the attempted treatment. The disease is characterized by deposits of bony calcium phosphate stones near the joints of the phalanges. In the author's cases the blood serum values for calcium, phosphorus, and uric acid were within normal limits. Many hormonal extracts have been tried in treatment of the disorder without success. Recent therapy has been directed toward mobilizing calcium by means of disodium hydrogen phosphate, ammonium chloride, sodium citrate, ketogenic diet, and parathyroid extract.—C. P.

VOLLMER, H.

Treatment of rickets and tetany by parenteral administration of one massive dose of vitamin D. *J. Pediat.* 16: 419. 1940.

Vollmer advises the intramuscular injection in one dose of 600,000 U of vitamin D in a mixture of 0.6 cc. of peanut oil and 0.4 cc. of ether. This has the same effect on rickets and tetany as the same doses of vitamin D when administered by mouth. The serum calcium and phosphorus become normal usually after 3 to 7 days. Tetanic convulsions cease within 24 hours and the calcium deposition in the bones is evident by x-ray at the end of one week. No local infiltration nor systemic damage has been noted. There are no calcium-containing casts in the urine.—M. B. G.

PINEAL

GERSTLEY, J. R., J. KASANIN AND E. LOWENHAUPT.

Teratoma of the pineal body. *J. Pediat.* 17: 512. 1940.

The eighteenth case of pineal teratoma is reported in a boy of 11 years of age. Autopsy revealed that one part of the tumor comprised a spongioblastoma multiforme which invaded the surrounding structures and spread widely throughout the brain. The early diagnosis offered difficulty and suggested either encephalitis or schizophrenia. The symptoms consisted of pubertas praecox, initial symptoms of pituitary cachexia, emotional changes and finally, signs characteristic of the involvement of the quadrigeminal plate and hypothalamus.—M. B. G.

THYROID

BEUKEMA, W.

A case of nervous cretinism. *Geneesk. tijdschr. V. Nederl.-Indië* 80: 2155. 1940.

An instance of nervous cretinism is described in a 10-year-old Dayak female, living in Central Borneo, an area where goiter is highly endemic.—W. Rudolfs.

KERLEY, C. G.

End results in the cretin. *Arch. Pediat.* 57: 432. 1940.

Two cases of congenital myxedema of the textbook type are presented with detailed histories and illustrations. Both these children pass as physically and mentally normal in school contacts and social activities. Six other ♀ cretins who have been under observation since infancy are now normal individuals as regards height, weight and mental endowment. They range in age from 40 years to 16 years. They are in good physical health and occupy social planes according to birth; only the immediate families are aware of the congenital dyscrasia. The end results were acquired by the administration of desiccated thyroid (Parke, Davis and Co.) in subtoxic dosage carried on under controlled medical observation in families sufficiently privileged to supply adequate home care.—Author's abstract.

KUNSTADTER, R. H.

Experience with benzedrine sulfate in the management of obesity in children. *J. Pediat.* 17: 490. 1940.

Benzedrine sulfate was administered to 30 obese children between the ages of 2½ and 16 years who had failed to lose weight on a reducing diet and desiccated thyroid substance. The initial dose was 5 mg. per day regardless of the age of the patient and the optimal dose between 10 and 30 mg. daily. The weight loss with continuous treatment over 2 weeks was 0.831 lb. per week. The weight

loss was primarily due to loss of appetite with subsequent decrease in food intake. Withdrawal of the drug or decrease in the dose usually resulted in a return of appetite and increase in weight. In a few cases, tolerance to the drug necessitated an increase in dosage. Variable effects were noted on the pulse rate and blood pressure, and little or no variation in the B.M.R. was noted. Unpleasant reactions experienced consisted of dizziness, abdominal pain, headache, insomnia, nausea, vomiting, nervousness, fainting spells and substernal pain. The author considers that benzedrine sulfate is frequently an effective adjunct in the management of obesity in children.—M. B. G.

McDonald, J. W., A. W. Brown and I. P. Bronstein.

Background and social adjustment of thyroid deficient children receiving glandular therapy. *Am. J. Dis. Child.* 59: 1227. 1940.

The background and social adjustment of hypothyroid children who had received glandular therapy for several years was examined. These children had a wide range in intelligence extending from very defective to average, with the majority in the high grade mental defective group. They were able to establish habits and play interests in accordance with those of normal children of the same mental age. The children having the most difficulty in adjusting to other children were between the ages of 7 and 12 years. Glandular therapy was effective in helping these children to make a better social adjustment. The adjustment of the older group, between 17 and 21 years, suggested that even with low intelligence, children with thyroid deficiency were able, with treatment and with proper attitudes towards them, to be partially self-supporting and to be helpful in the home.—*M.B.G.*

Martin, L.

The basal metabolism test in thyrotoxicosis. *Brit. M. J.* 1: 927. 1940.

Virtually all cases of thyrotoxicosis have a raised B.M.R.; but hypermetabolism is only a part of the symptom complex, and is neither a sound index of severity of any particular case nor a reliable standard of comparison. For diagnostic purposes it is confirmatory in florid and masked cases, where a normal reading is a warning against thyroidectomy. As a means of indicating the right moment for thyroidectomy during preoperative therapy or checking progress during x-ray therapy it does not surpass clinical observation, but it is a valuable means of indicating postoperative myxedema before symptoms appear.—Author's summary.

Miller, H. G.

Myasthenia gravis and the thymus gland. *Arch. Path.* 29: 212. 1940.

Miller discusses the association of tumor of the thymus and myasthenia gravis, first described by Weigert in 1901. Weigert called the thymic lesion a lymphosarcoma and looked on the lymphorrhages in the voluntary muscles as metastases. This viewpoint has been disproved by numerous authors. Miller reviews 5 cases of myasthenia gravis encountered among 16,300 autopsies at the Johns Hopkins Hospital. In 2 cases encapsulated tumors of the thymus were found, with remnants of normal thymus outside the capsule; in 2 the thymus was persistent, with well marked peripheral epithelial hyperplasia in 1 instance, and in 1 case the thymus was not identified. This investigation brings the total number of cases in which a lesion of the thymus was discovered to 41, in a series of 87 cases of myasthenia studied. Miller suggests that patients with myasthenia gravis be subjected to careful roentgen examination and that irradiation and surgical removal be employed more frequently because of the unfavorable progress under even the newer methods of therapy.—Abstract, *Arch. Neurol. & Psychiat.*

Newton, A. H.

Goiter in northern California. A survey of 175 thyroid operations. *California & West. Med.* 53: 261. 1940.

Endemic goiter is highly prevalent in northern California where the northern coast ranges join the Sierra Nevada ranges, extending from Del Norte throughout Siskiyou and Modoc counties.—M. L. Ilsley.

Regan, J. F., and R. M. Wilder.

Hyperthyroidism and diabetes. *Arch. Int. Med.* 65: 1116. 1940.

Sixty-one cases are added to the 38 reported by Wilder in 1926. In the interim the incidence of diabetes as a complication increased from 1.1 to 3.2%. As before, the occurrence was more frequent in adenomatous goiter with hyperthyroidism (5.6%) than in exophthalmic goiter (1.7%), possibly explained by the fact that exophthalmic goiter occurs in younger patients. Because of uncertain onset of each disease and since certain symptoms are common to the two, conclusions as to priority of appearance were not satisfactory, although in many instances, as judged by case histories, the hyperthyroidism appeared first. The data suggest that patients who receive satisfactory surgical treatment for the hyperthyroidism do as well as patients with diabetes alone; the prognosis is unfavorable for those not relieved by operation.—From J.A.M.A. abstracts.

Reilly, W. A.

Thyrotoxicosis. *Am. J. Dis. Child.* 60: 79. 1940.

A 10-year study of 62 patients who have had thyrotoxicosis for the past 25 years is reported. Only severe cases are included. The onset may be as early as 3 to 5 years of age but occurs most commonly between 12 to 14 years of age, and is arrested by the 18th year, with occasional recurrence at about the 30th year. A child never has a total remission but the disease "waxes and wanes" until full arrest. Etiological factors are familial occurrence, overactivity of the parasympathetic nervous system, infection, adolescence and emotional upsets. The statural growth is more rapid before the onset of toxicity. The epiphyseal age is accelerated, depending upon the degree of toxicity, so that the more active the disease, and the longer the duration, the greater is the resultant giantism and acceleration of epiphyseal age. The second teeth also develop prematurely. Thyrotoxicosis tends to suppress ovarian function. The more active the toxicity, the longer the duration and nearer the onset to expected puberty, the more suppressed is sexual maturation. The B.M.R. cannot be relied upon as a criterion. Therapy consists of medical or surgical pro-

cedures. Medical treatment was successful in 45 cases and unsuccessful in 55 which went to operation. Rest in bed is not as efficient as rest in bed plus iodine in the form of compound tincture of iodine in dosage of one to five drops a day. Severe exophthalmic goiter rarely shows more than temporary improvement with the prolonged use of I. A mildly active case may become aggravated while I is being used. The use of I helps in the tendency to remissions. Operative procedure is the best method for severe cases and other methods only temporize in this type of a case. Radiation may be an aid to surgery. In 30 cases there were 12 recurrences and 3 questionable recurrences. Complications occurred in 12 out of 51 patients and consisted of hypothyroidism, thyroid crisis, myocarditis, osteoporosis, and hypoparathyroidism. It is questionable if sterility and failure to carry until term can be related to exophthalmic goiter which occurred in childhood. Reilly claims that if the disease is treated during childhood and adolescence it is arrested by the 18th year.—*M.B.G.*

Reinhoff, W. F., Jr.

Microscopic changes induced in thyroid gland by oral administration of desiccated thyroid: use of the substance in treatment of congenital and simple colloid goiter. *Arch. Surg.* 41: 487. 1940.

Six case histories of goiter are presented showing marked clinical improvement with treatment, checked by biopsy specimens of the gland. Changes induced in the gland by thyroid per os were from typical simple colloid goiter to diminution in size and number of follicles and paucity of colloid, with the majority of follicles empty, and evidences of disuse atrophy. A number of undefined cases are mentioned of large diffuse and soft nodular goiter associated with low B.M.R. successfully treated with orally administered thyroid in increasing doses over a period of months. In all cases goiter was reduced to normal size with restoration of normal B.M.R.—H.O.H.

Rowntree, L. G.

Thyroid therapy in juvenile myxedema. *J. Pediat.* 16: 771. 1940.

The author calls attention to the importance of thyroid function on growth and reports 2 cases in which desiccated thyroid substance produced startling results in 2 dwarfed children. In one case that of a girl of 7, the patient grew 20 in. in height and gained 57 lb. in weight over a period of 6½ years, on thyroid substance alone. The second patient, a girl of 15, gained 10 in. in height in 27 months on adequate doses of thyroid and anterior pituitary substance by mouth, in addition to injections of 'maturity hormone.'—M. B. G.

Shelton, E. K., B. N. Tager and Elizabeth Hoyt.

Cretinism. Case report. *Endocrinology* 27: 425, 1940.

A cretin girl 10½ yr. of age (ht. 36.2 in.; bone age 1 yr.) was treated for 4½ yr., as follows. During the first year an alkaline extract of anterior pituitary was injected in a dose of 20 R.U. daily. At the end of 1 year's treatment the bone age had not changed and the height increment consisted of 0.6 in., equivalent to the growth expectancy of this cretin without any therapy. During the 2d year, 1 gr. desiccated (U.S.P.) thyroid was administered daily, alone. A growth of 6 in. occurred and a carpal maturation to a level of 4 yr. appeared. During the 3d year the therapy was increased to a dose of 2 grs. thyroid daily. A further growth of 4 in. and a carpal development to a level of 8 yr. occurred during this interval. During the remaining 18 mo. of observation the child was maintained on 2 grs. of thyroid, supplemented by vitamin B complex, containing 1000 I.U. of B_1 daily. A further growth of 3.3 in. occurred and the bone age advanced to a level of 11 yr. Mental development was considerable, progressing from a 10-year-old inert child unable to talk or walk to a 15-year-old child capable of dancing, playing and infantile conversation, still lagging, however, far behind her physical development and actual age. The case demonstrates that pituitary therapy with a growth factor as here used stimulates neither growth nor development in a cretin. Adequate thyroid therapy causes the maximal spurt in growth and development during the 1st year of treatment; subsequent increase in thyroid dosage and vitamin B supplementation did not appear to enhance the results. It is emphasized that repeated bone age studies are of great value in the regulation of thyroid therapy in cretinism.—*E. K. Shelton.*

Topper, A., and H. S. Rubin.

Basal metabolism of tuberculous children. *Am. J. Dis. Child.* 59: 535. 1940.

Studies were made on the B.M.R. of 70 children with tuberculous pleurisy, 40 of whom had an associated active primary tuberculosis. The majority of these children had an increased B.M.R., ranging from+14 to +53%, with an average of +25%. The metabolism in many of these patients was found to be normal when the infection was inactive. Pleural effusion without demonstrable parenchymal or glandular involvement or thickening of the pleura was without effect on the B.M.R. The authors conclude that active tuberculosis of the primary type is usually associated with increased heat production.—*M.B.G.*

Velde, J. Van de.

The results of treatment with antithyroid serum. *Rev. belge sc. med.* 11: 20. 1939.

Experimental treatment of 600 patients showed that blood or serum of thyroidectomized animals was efficacious in the therapy of hyperthyroidism, improving the clinical symptoms and increasing the weight, although not reducing the metabolic rate. This was partly due to a thymic hormone and partly to unknown substances. The treatment is useful in preparation for surgery or as an adjuvant to radiotherapy.—J. B. Bullitt.

Welch, C. S., and A. C. Broders.

Golgi apparatus of the thyroid gland. *Arch. Path.* 29: 759. 1940.

A study of the Golgi apparatus was made in 73 cases of goiter. Hypertrophy was noted in 34 of 35 glands removed from patients with exophthalmic goiter, and in 19 of 21 glands removed from patients with adenomatous goiter with hyperthyroidism. However only 5 of 16 goiters in patients with adenomas who did not have hyperthyroidism showed an enlargement of the Golgi apparatus.—L. B. Shpiner.